HEREDITY AND DISEASE

Heredity and Disease

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PREFACE

THE present book is an attempt to arouse interest among general readers in our modern knowledge of heredity, particularly in the rôle played by the hereditary factors in bringing about disease conditions of various kinds. Though particular stress has been laid upon simplification in order to make the evidence readily intelligible, at the same time considerable attention has been paid to give a sufficiently clear presentation of the mechanism behind the hereditary phenomena, so that the reader who wants real information may become familiar with the underlying general principles. It is therefore hoped that the book may also prove useful to medical students and physicians as an introduction into a field that is of constantly increasing importance for the science of medicine.

An enormous amount of data on hereditary cases has accumulated during recent years within the different branches of medicine. It is not intended to give anything like a full account of this large body of evidence here. But a considerable number of the best-established

cases has been selected which serves for the purpose of illustrating the different hereditary principles dealt with. For further special information as well as for literature references the reader is referred to some of the larger text-books now in existence. The titles of several of these are given in the Appendix.

In a concluding chapter some general bearings of heredity on human affairs are briefly discussed. This discussion, which is necessarily rather fragmentary or restricted to suggestions, is consciously influenced by the writer's personal opinions.

During the autumn of 1933 the writer delivered the series of Edward K. Dunham lectures at the Medical School of Harvard University on "Genetics and Pathology." The present book is an outcome of these lectures. The writer should be glad if this little book might be accepted as a modest return for the great kindness and hospitality extended to him during that unforgettable sojourn.

The author wishes to express his indebtedness to his colleagues for assistance in different ways; to Miss S. Mörch who has prepared most of the line-cuts and diagrams; to Professor L. C. Dunn for his kindness in reading the English manuscript; and, last but not least, to the publishers, W. W. Norton & Company, Inc., for their personal interest and great assistance in the preparation of this book.

Otto L. Mohr.

Oslo, *August*, 1934.

HEREDITY
AND
DISEASE

CHAPTER I

GENERAL INTRODUCTION

1. HEREDITARY FACTORS AND PERSONAL CHARACTERS

BY the term *heredity* we mean that characters, physical or mental traits, which are present in parents or more remote ancestors, reappear among the descendants in succeeding generations. This is such an everyday experience that, almost without being aware of the problem involved, we simply take it for granted that "He has his nose from his father," or "She is her own grandmother all over again." The science of *genetics* aims at explaining how and why such a transmission of characters may take place.

Whatever an individual inherits from its parents it receives through the two *gametes,* or marrying cells, that meet and fuse during fertilization. But these germ cells, the egg cell and the sperm, which represent the only connecting link between two succeeding generations, do not exhibit a single one of those characters which distinguish the individual to which they give

origin. They do not possess any nose, eyes or particular mental properties. Hence it cannot be the characters as such that are transmitted. But the germ cells contain particular hereditary factors, the *genes,* which exert their action in the course of the individual development and thus determine all the hereditary *characters,* physical or mental, that mark the individual.

It is of foremost importance that from the very outset we should be aware of this fundamental distinction between genes on the one hand and characters on the other. A child whose hands and feet exhibit the character polydactyly, extra fingers and toes, has at fertilization received a gene for the development of this abnormality from one of its parents. A person whose eyes exhibit the character brown eye color has correspondingly received a gene for development of brown eye color from one or both parents. *Each hereditary character, normal or abnormal, is determined by one or more such hereditary units, the genes.*

The sum total of all the genes an individual receives at fertilization we denote as the *genotype* of this individual. Thus our total hereditary equipment is irrevocably determined at the truly historical moment when the sperm and the egg cell meet. But when we speak of *the sum total of all our personal characters,* our *phenotype,* the situation is quite different. The pheno-

type of an individual comprises also a large series of characters, details of structure or behavior, that have nothing to do with heredity. During the pre- and post-natal development a wide series of external, environmental influences, such as nourishment, training, diseases, etc., exert their modeling and modifying influence.

A person may inherit genes which determine that he has an ear for music. But the ability to play the piano he must *acquire,* namely, by exercise or training. He may carry genes for a perfectly normal development of the skeleton. But if the nourishment during early childhood is deficient in particular vitamines, he may develop skeletal abnormalities which will remain throughout all his later life and represent part of his phenotype.

My personality, my *phenotype,* is in other words a *product of two different sets of influences,* the internal ones involved in the genes, and the external ones involved in the surroundings, the environment in the broadest sense of this word. Phenotype and genotype are entirely distinct notions that must not be confused.

When, in spite of the untiring efforts of the human mind, it has been reserved to our own time to see the problem of inheritance solved, this has first and foremost been due to the clearing up of the previous ob-

scurity in this particular field. Misconceptions are very apt to arise. No wonder that our predecessors believed congenital syphilis or infant tuberculosis to be inherited. *We* know that these diseases are not due to genes present in the germ cells, but to infection with particular microbes, and that this infection may—and in the case of syphilis frequently does—take place already in the unborn child.

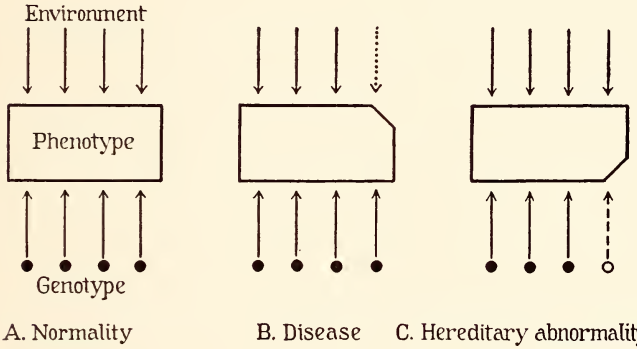
Osvald in Ibsen's *Ghosts* had not inherited his syphilis, as Ibsen believed. He had received the infection from his mother, who herself had caught it from her husband. For the dramatic economy of the play this is of course entirely irrelevant. Children from parents with tuberculosis are so exposed to infection that they not infrequently develop the disease during early infancy. Genes which produce syphilis or tuberculosis do not exist; these diseases are due to environmental agencies, in this case to microbes.

As other striking examples of the modeling influence of the environment certain plants may be quoted which, though of the same genotype, are encountered in two exceedingly different-looking forms, one terrestrial and one aquatic, according to whether they are grown in dry or moist surroundings. Further, the female type of plumage in our common domestic fowl is not genotypically determined, but is due to the in-

hibiting action of the ovarian secretions. If, as shown by Goodale, the ovary is removed, then male plumage appears, irrespective of the sex of the body.

2. HEREDITY AND DISEASE, BASIC CONCEPTIONS

In the above introductory discussion of the concepts gene and character we have in quite a few cases used disease conditions, pathological states, as illustration. Let us now for a while consider what disease means from a biological point of view.



1. Diagram illustrating how deviations from normality may be caused, either by a change in the environment (B), or by a change in one of the genes (C). Upper row of arrows indicate the environmental influences, lower row the action of the genes.

Following Lenz we may begin by emphasizing that the organisms of to-day have from time immemorial been subjected to the filtering process of natural selection. As a result of this process each organism is highly

adapted to its proper environment. If changes in this environment, *external* influences such as infections, lack of vitamines, disfunction of a gland with internal secretion, etc., interfere with this balance of adaptation, the organism is said to be sick, suffering from a *disease* (Text-fig. 1, B).

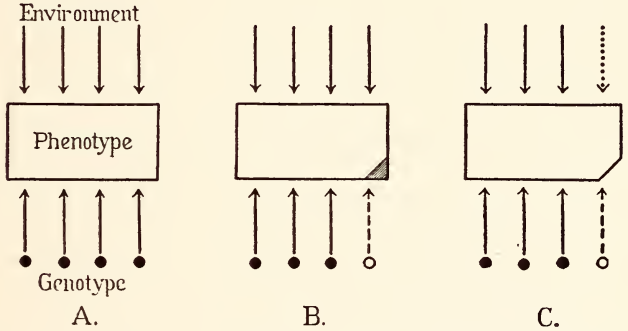
But the balance of adaptation may also be upset by *internal* influences. If one of the hereditary factors governing a particular link in pre- or post-natal development has undergone an unfavorable change, then the result will be anatomical or physiological deviations, *abnormalities,* which may also seriously interfere with the normal adaptation (Text-fig. 1, C).

Both these fundamentally different classes of deviations from normality are grouped under the general heading *pathological states,* though in using this term we are of course aware that strict boundaries between the ideas of health and normality on the one hand, disease and abnormality on the other, happily do not exist. Each organism must be allowed a fair range of variation.

For the sake of clearness it would be a great advantage if we were able to reserve the word "disease" for those pathological states that are due to non-hereditary, environmental agencies, infections, injuries, etc. The term "hereditary disease" is unfortunate and apt to

cause misconceptions. The internal agencies, the unfavorable genes, induce hereditary defects, abnormalities, anomalies, and they may also by weakening the organism lower the resistance to particular diseases. Under the present usage, however, it is hardly possible to adhere to this distinction consistently.

In medicine attention has until recently been focused on the reactions of the organism to changes in the environment. In this book we intend to concentrate our attention on the other side of the picture, on the rôle which the genes play in bringing about disease conditions of various kinds.



2. An unfavorable gene may fail to produce detectable external changes (B). But if the environment changes the effect of the gene may become manifest (C). Symbols as in Text-fig. 1.

A clear realization of the *interaction* of genes and environment is particularly important in this connection. Quite a few genes fail to have any visible effect

under ordinary conditions (Text-fig. 2, B). But if the environment changes, the gene will manifest its effect (Text-fig. 2, C). A single example may serve as an illustration. A particular type of hypertrophic, horn-like nails (*onychogryphosis*) is distinctly hereditary. But the anomaly does not develop except in the particular environment created by the wearing of shoes. Hence, the anomaly only affects the toes in grown-up people, never the finger nails (see Plate I, Fig. 1). We are here confronted with the phenomenon of *hereditary disposition,* what medical men call *hereditary diathesis,* in its simplest form.

From what has been said already it will be understood that, in order to get a real understanding of the hereditary phenomena, we must go a round-about way and for a moment concentrate our attention on the germ cells which contain all the hereditary factors which are passed on from one generation to the other.

CHAPTER II

THE PHYSICAL BASIS OF HEREDITY

1. THE MECHANISM OF CELL DIVISION. THE CHROMOSOMES

ALL living organisms are built up of *cells,* which are, as a general rule, minute invisible units. All organisms with sexual reproduction also develop from a single cell, the *zygote,* or fertilized egg cell, resulting from the union of one egg cell and one sperm.

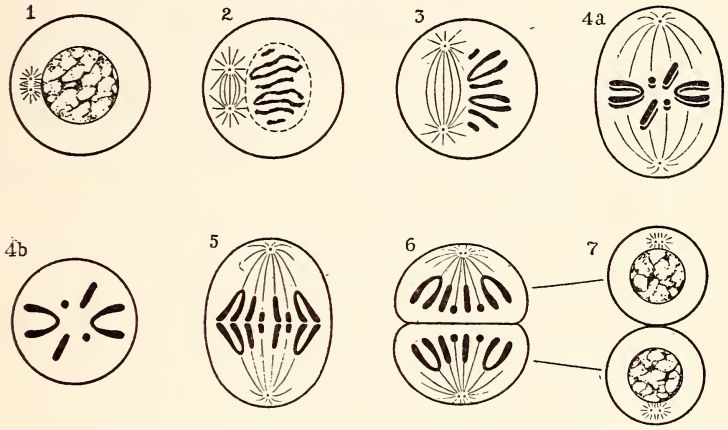
After fertilization the egg cell immediately starts to divide, first into two daughter cells of equal size, then each of these again divides in two, and so on, so that after a short time an embryo is formed, consisting of many cells, every one of which is derived from the one fertilized egg cell. During the further development the new-formed cells arrange themselves according to particular laws forming the different tissues and organs. But the growth of the individual is all the time due to successive divisions (in two) of those cells which have previously been formed.

In the fully developed organism the single cells have different forms and structures according to the different tasks they are to accomplish in the household of our body (connective tissue cells, muscle cells, nerve cells, etc.). In *one* respect, however, all cells are fundamentally alike: each consists of a *cell body* (a kind of matrix of semi-fluid *cytoplasm*) and a so-called *nucleus,* a denser roundish body lying in the middle of the cell, like the stone in a cherry (Text-fig. 3, 1). This kernel is the center of vital activity upon which the maintenance and especially the reproduction of the cell depend.

If we examine the nucleus when a cell is about to divide, we are confronted with one of the most fascinating spectacles encountered in organic nature. The nuclear substance, which at this time is recognizable by its sharper delimitation and greater density of its granular parts is found gradually to arrange itself into very distinct V-shaped, hook-shaped, rod-shaped or tiny spherical bodies, which eagerly absorb certain dyes. For this reason they are called *chromosomes,* which simply means colored bodies (Text-fig. 3, 2-6).

These chromosomes with surprising orderliness now arrange themselves in the equatorial plane of the cell, forming a rosette-like *equatorial plate* (Text-fig. 3, 4a, 4b). In this stage every single chromosome is split

lengthwise with absolute accuracy, after which the daughter chromosomes thus produced separate and are pulled towards opposite cell poles (Text-fig. 3, 5-6). This separation is governed by very tiny fibers in the cell body. These fibers, the *spindle-fibers,* irradiate



3. Diagram of the cell division. 4 a, side view of the equatorial plate with the chromosomes split lengthwise. 4 b, the equatorial plate seen from above.

from two dot-like *centrioles* and attach themselves to the chromosomes. In the middle face of the cell division they form a spindle-like formation, the central spindle, which represents the cell's own division apparatus.

When the daughter chromosomes have reached their respective poles, the chromosomes disintegrate and their substance, the *chromatin,* again forms a

roundish cell nucleus (Text-fig. 3, 7). At the same time the cell body has also undergone a constriction in the region of the equatorial plane, and when the two daughter nuclei have been formed, this constriction cuts through, so that the entire cell is now divided into two daughter cells, each with its own nucleus.

Why does nature set going such a complicated series of processes in order to attain the rather simple object of having one cell divide into two? If we consider the matter, we will realize that the mechanism described ensures in a most ingenious way, not only that the two new-formed nuclei receive an exactly *equal share* of nuclear substance, but that the amount which they receive is also of exactly the *same kind*. Clearly, the nuclear substance must be very important, since such elaborate provisions are made that the resulting daughter cells shall be both quantitatively and qualitatively equivalent in this respect.

Since all the cells of an individual through a shorter or longer series of cell divisions of this type are derived from the fertilized egg cell, it follows that all the body cells must contain an equal amount of chromatin of the same kind. This is confirmed by actual observation. Whenever a cell divides, exactly the same number of chromosomes is seen to be present in the equatorial plate. And this *constant chromosome num-*

ber is not only typical of the individual in question, it is also typical of all individuals belonging to the same species. *Every species has its characteristic chromosome number.*

And, what is still more surprising: This chromosome number is always a *paired* number, 8 in a particular fly, 30 in a species of grasshoppers, 60 in the horse, 48 in man, 14 in peas, 24 in the tomato, 20 in maize, to mention only a few scattered examples. More than that, in favorable material it may be demonstrated that *the chromosomes, according to their individual size and shape, may be arranged in pairs of homologous members,* partners, so to speak. The entire chromosome complement of a cell in other words comprises two homologous series, which correspond to each other like mirror images (see Text-fig. 3).

The questions arise: Why a paired number? Why two homologous series of chromosomes? The simple explanation of this truly remarkable situation is found when we consider the maturation of the germ cells and the fertilization process.

2. THE MATURATION OF THE GERM CELLS AND THE MECHANISM OF FERTILIZATION

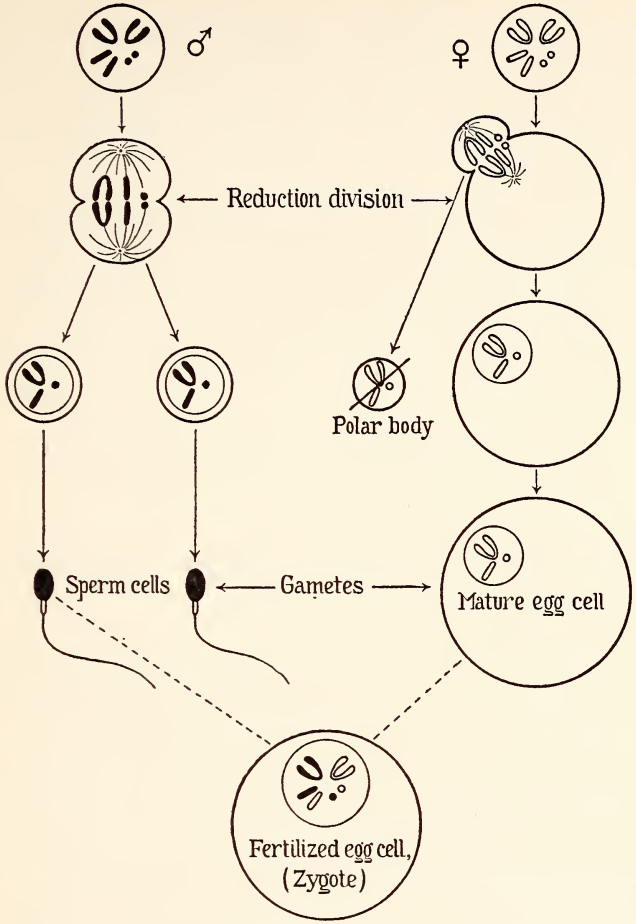
We have already mentioned that all our cells are derived from the *fertilized egg cell,* the *zygote,* which

results from the fusion of two cells, the female egg cell and the male sperm. If these ripe germ cells also had the same chromosome number as our body cells, then the fertilized egg cell resulting from their fusion, as well as the individual developing from this egg cell, would contain twice as many chromosomes as the parents. We seem in other words to be confronted with a contradiction.

An examination of the ripening germ cells solves this difficulty. It turns out that the mature germ cells, the egg cell and the sperm, *differ from all other cells by having only half the chromosome number of the species.* In one of the last two divisions of the ripening germ cells, the so-called *reduction division,* the chromosomes do *not* split lengthwise. On the contrary, after a temporary lengthwise union, or *synapsis,* the two members of each chromosome pair disjoin, segregate and pass undivided to opposite daughter cells (Text-fig. 4).

The ripe germ cells which develop from these daughter cells, will accordingly *receive only half the chromosome number of the body cells,* viz., one of the two homologous series typical of the species.

In the details of the process there is a difference among males and females (see Text-fig. 4). In the males both daughter cells are equivalent and develop



4. The maturation of the germ cells and the process of fertilization. Female chromosomes outlined (white), male chromosomes solid (black). (A second maturation division in which the chromosomes are split lengthwise is disregarded in the diagram. In this division the number of sperms is doubled, and the egg cell gives off a second polar body; but the chromosome number remains unchanged.)

into functional sperms. In the females, however, only one of the two daughter cells is transformed into a functional egg cell, rich in stored yolk material. The other, the so-called *polar body,* is rudimentary and soon degenerates.

Applied to a species with 6 chromosomes, the situation is as follows: The ripe egg cell and the sperm will have only half this number, viz., 3. In fertilization, the union of one egg cell with one sperm, we have accordingly:

egg cell		sperm		fertilized egg cell
3	+	3	=	6

i.e., the paired chromosome number of the species is again restored.

Now we may understand why the chromosomes always occur in pairs of homologous members in the body cells. These cells are all derived from the fertilized egg cell by simple cell divisions. They have accordingly all received, we might well say inherited, one paternal set of chromosomes through the sperm and a corresponding maternal set through the egg cell.

The fertilization process is in other words a double safeguard. The ripe germ cells, the *gametes,* are single structures; the fertilized egg cell, or *zygote,* as well as the individual developing from this cell is a double

structure, in which the paternal and maternal organisms, through the chromosomes, are equally represented. Technically, the *gametes* are said to be *haploid* with respect to chromosome equipment, in contrast to the *zygote* and the body cells, or *somatic* cells, which are *diploid. This fundamental difference between germ cells and body cells is established in the reduction division which occupies a truly unique position among all cell divisions.*

In the moment of fertilization the fate of the new individual is irrevocably determined, genetically. The germ cells represent the only connecting link between the generations. They lose every connection with the parental organisms. Even in forms where the embryonic life is spent inside the mother's body, as for instance in man, the egg cell is set free from any connection with the mother, being discharged from the ovary into the abdominal cavity. If it is fertilized in the course of its journey down the oviduct, it will take up its quarters in the uterus and spend the first nine months of life there, as a parasite, an independent organism inside the mother organism. Even the blood of the mother does not enter the fœtus.

As regards external characteristics the egg cell and the sperm are as different as cells may possibly be. The tiny sperms are provided with a very efficient

power of locomotion that enables them to find and to penetrate into the yolk-rich, motionless egg cells which are among the largest cells known. In *one* respect, however, we have seen that the two kinds of germ cells are equivalent, that is, in their nuclear material, chromosome equipment.

When we consider this fact and remember the surprisingly orderly distribution of the chromosomes in every single one of the millions of millions of cell divisions, during the maturation of the germ cells and at fertilization, we realize that the idea could not be remote, that these microscopical elements, the chromosomes, represent the physical basis of the hereditary material. But its correctness can only be tested, and *has,* as we shall see, actually been proved, by the aid of breeding experiments.

Before we enter on a discussion of this evidence it remains, however, to mention a particular microscopical finding of Henking, which in the hands of McClung, E. B. Wilson and Miss Stevens led to the solution of the age-old riddle of sex determination.

3. THE MECHANISM OF SEX DETERMINATION. SEX DETERMINATION IN MAN

THE question how, and at what time the sex of an individual is determined has through all ages capti-

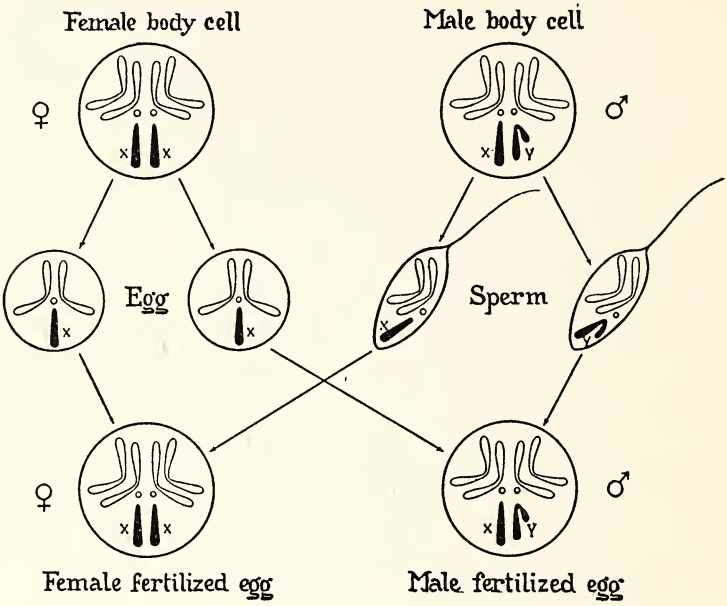
vated the human mind. What is it, for instance, that in man decides whether the coming child will be a girl or a boy?

In few fields of biology have as many and as varied attempts at explanations been advanced. Thus, according to a German scientist, no less than about 500 different sex determination theories had been advanced up to the beginning of the last century, theories which all turned out to be so many testimonies of the insufficiency of the free human imagination, when facts are lacking.

Not until our own generation was the simple solution discovered, and strangely enough not by aid of experiments, but by microscopical examination of the germ cells themselves.

During these germ cell investigations, the main results of which have been presented above, it turned out that there is *one* exception to the rule that the body chromosomes always occur in pairs of homologous members. In the males of many animals including man a single pair exists which in contrast to all the rest comprises two *non*-homologous members, the X- and the Y-chromosomes, of which the latter differs both in size and shape from the X. In the female, however, the corresponding pair consists of two homologous X-chromosomes. In a species with 8 chro-

mosomes the female body cells contain accordingly 6 + XX, the male cells 6 + XY (see Text-fig. 5). These chromosomes are called the *sex chromosomes* in contrast with the other pairs which are known as *autosomes.*



5. The mechanism of sex determination in a species with 8 chromosomes. The sex chromosomes, XX in female body cells, XY in male body cells, solid (black); all the other chromosomes outlined (white).

During the maturation of the female germ cells the two members of the female X-chromosome pair disjoin in the reduction division and enter opposite daughter cells. *All ripe egg cells will accordingly be of*

the same kind, containing one X-chromosome. But during the maturation of the male germ cells the situation will be different. Here the X and the Y disjoin in the reduction division, so that *two kinds of sperms are formed, one half containing an X-, the other half a Y-chromosome.* (Text-fig. 5.)

During fertilization two alternatives accordingly exist: either the egg cell, which always contains an X, may be fertilized by an X sperm, in which case an XX individual, a female results; or the egg cell with its X is fertilized by a Y sperm. Then an XY individual, a male, is formed.

Applied to the example, Text-fig. 5, a species with 8 chromosomes in all, the female body cells have 6 autosomes + XX, the male 6 autosomes + XY. The ripe egg cells contain half this number, viz., 3 + X, while the sperms are of two different kinds, those with 3 + X, and those with 3 + Y respectively. During fertilization the situation is accordingly as follows:

egg cell sperm zygote

$(3 + X) + (3 + X) = 6 + XX$, a female

or, $(3 + X) + (3 + Y) = 6 + XY$, a male

The sex of the individual is accordingly determined automatically during the fertilization process. The outcome depends upon which one of the two kinds of

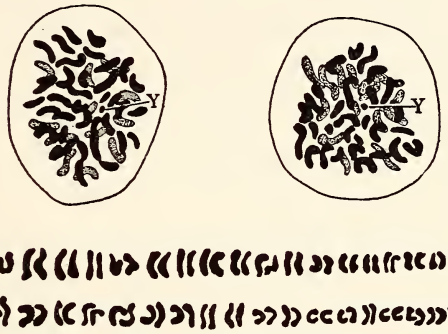
sperms happens to fertilize the egg cell. Since the X- and Y-sperms are formed in equal numbers, an equal number of females and males will be produced.

In quite a few forms a Y-chromosome is lacking entirely, so that here the females are XX, the males XO. All the ripe egg cells will contain an X, since a pair of X's is present at the reduction division. As regards the sperms, half of these will contain an X since the single X-chromosome passes undivided to one of the daughter cells in the reduction division. The other half of the sperms will accordingly receive no sex chromosome. The sex determination mechanism remains in principle the same: If the egg cell with its X is fertilized by an X sperm, a two-X individual, a female, results; if it is fertilized by a sperm with no X-chromosome a one-X individual, a male, is formed. This may be readily understood by inspection of Text-fig. 5, if the Y-chromosome is disregarded.

It must also be added that in some forms, notably birds and butterflies, this sex determination mechanism is in a way reversed, in so far as here the females have the XY, the males the XX combination of sex chromosomes.

As regards the human material, with its unfortunately large number of minute chromosomes, competent observers now agree that the diploid chromosome

number of the body cells is 48. And thanks to the work of Painter, Evans and Swezy, and Minouchi, it may probably be regarded as established that man belongs to the XX–XY type (see Text-fig. 6). In other words the body cells of women contain 46 autosomes + XX. those of men 46 autosomes + XY.



6. The human chromosomes. Above are the chromosomes in equatorial plates from male individuals. Y, the small roundish Y-chromosome. Below are the chromosomes arranged according to size. Upper row, the male complement; the unequal XY sex chromosome pair seen to the right. Lower row, the female complement; the two homologous X-chromosomes seen to the right. AFTER EVANS AND SWEZY.

All the egg cells will accordingly contain half the above number, viz., 23 + X, while two kinds of sperms are produced, 23 + X and 23 + Y, respectively. Hence, at fertilization two alternative possibilities are at hand:

egg cell sperm zygote

$(23 + X) + (23 + X) = 46 + XX$, a girl

or, $(23 + X) + (23 + Y) = 46 + XY$, a boy

Now some one may perhaps object that they know of quite a few families with boys or girls only. This is because this alternative mechanism works in accordance with the laws of probability. It may very well happen that, from a mixed stock of playing cards, we may draw only red cards or only black cards, say six or seven times in succession. But if we keep on long enough the number of black and red cards will even up. The same in human families: If we add the children from many families, so that we obtain large enough numbers, then the number of boys and girls will be roughly equal.

The question as to whether we may by special methods *intentionally* increase the number of either boys or girls must be answered in the negative. Such a change in the sex-ratio has been induced experimentally both in some plants and in certain lower animals. But the forms in which this has been attained differ in particular and important respects from man and other mammals.

In the latter forms the methods suggested have as their object to give either the X-sperms or the Y-sperms an advantage in the competition; and it can not be denied beforehand that this might eventually be possible. But many sources of error are involved. And the alleged positive evidence so far obtained is by

no means convincing. At any rate, we can never expect more than to influence somewhat the *probability* of obtaining one sex in preference to the other. The prospect of ever being able to determine beforehand the sex of the coming child may safely be regarded as nil.

CHAPTER III

THE ESSENTIAL PRINCIPLES OF INHERITANCE AND THEIR MECHANISM

1. GREGOR MENDEL AND THE MENDELIAN LAW OF HEREDITY. THE GENES

LONG before the above knowledge of the fertilization process and the maturation of the germ cells had been attained, the fundamental law of inheritance had been disclosed by experimental analysis.

This first-rate achievement in the history of science we owe to *Gregor Mendel,* not an obscure, modest monk as legend makes him, but an active, commanding personality, in later life as abbot of the rich monastery at Brno, Czechoslovakia, a real prince of the Church.

He was an outsider, that is true, but a scholar with a broad training in classics and history, and in different lines of science as well. The latter studies he had carried out during a two-year sojourn at the Vienna University. Though a genius of supreme brilliancy,

he failed at the University examinations—no less than twice. This is one of the strange paradoxes which may afford consolation to quite a few. But every line of his famous treatise bears witness to the trained scientist, not the haphazard worker.

Moreover, he lived in a favorable environment in the daily company of a selected group of gifted and highly educated men who, like Mendel himself, served as professors and teachers in the high schools, not only in humanistic, but also in pure scientific discipline (see Fig. 3, Plate I).

The great tragedy in his life is the fact that he was too far ahead of his time. Not one of those to whom he sent his treatise was able to grasp its tremendous importance. To this was added during the later part of his life the pathetic, year-long political struggle for what he believed to be the right of his monastery. The government had imposed a tax on this institution, which Mendel, then abbot, felt conflicted with the Constitution. This hopeless fight ended by making the kind and broad-minded man a sore and isolated misanthropist. Disappointed in his scientific work as well as in his belief and trust in men, he died unknown in 1884. To quote a Norwegian poet:

Is it not to heart, to genius and to misfortune,
That God gives the most beautiful garlands of immortality?

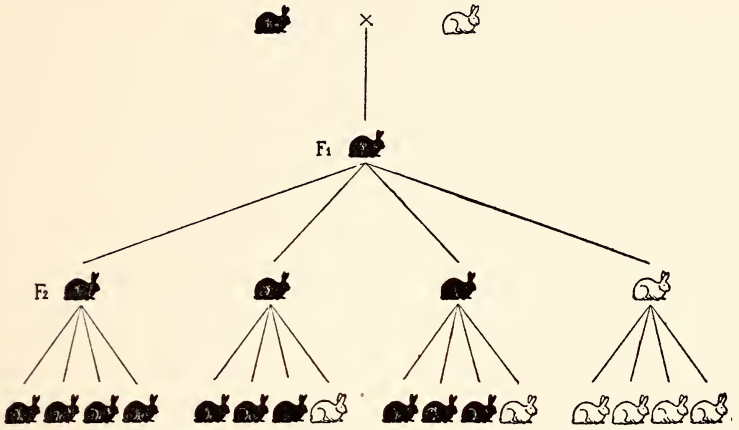
At the dramatic rediscovery of Mendel's work in 1900, simultaneously made by Correns, Tschermak and de Vries, the time *was* ripe. And from then it was not long until it was demonstrated that Mendel's basic principle of heredity was of general bearing throughout the entire plant and animal kingdom, man included. The first case in human material was a hereditary malformation, a shortening of fingers and toes, published in 1905 by Farabee, then working in Professor Castle's laboratory (see Plate I, Fig. 2).

Before this a young American medical student at Columbia University, the late Dr. W. S. Sutton, was able to demonstrate, in a brilliant contribution, how our knowledge of the distribution of the chromosomes provided us with an adequate mechanism for an explanation of the marvelous numerical consistency of the Mendelian law of inheritance. This was at the time a real achievement which should be remembered when we deal with the bearings of genetics on medical science.

Mendel himself worked with peas. For an illustration of the general law discovered by him, we shall choose the following example from animal material (see Text-fig. 7):

If we mate a pure-bred colored, say black, rabbit with a white (albino) rabbit, all the offspring in the

first, the so-called F_1 generation, will be colored. If these colored F_1 animals are bred together, we obtain in the next, the F_2 generation, *both* colored and white rabbits, and curiously enough in a definite *ratio,* viz., ¾ colored: ¼ white, i.e., a 3:1 ratio (see Text-fig. 7).



7. Cross of a colored rabbit with a white (albino) rabbit. F_1, first generation, all the offspring colored. F_2, second generation, colored and white rabbits in the ratio 3 : 1.

Further, when the white rabbits are bred together, they themselves as well as all their offspring give white offspring only; they are pure, *homozygous,* in this respect. The three quarters of colored offspring, however, behave otherwise. One of them is pure, by inbreeding giving colored offspring only. But the remaining two quarters (in the middle of the diagram) are, like their parents, found to be of mixed, *heterozy-*

gous, genotype: when inbred they give colored and white offspring in the ratio ¾ : ¼. Their hybrid, heterozygous constitution may also be demonstrated by mating them to their white brothers or sisters, this cross giving black and white offspring in the ratio ½ : ½, i.e., in equal numbers.

The fundamental principle disclosed by Mendel by aid of a variety of plant experiments of this type may be expressed thus: *Contrasting hereditary characters, which are combined in one individual by crossing, are each conditioned by independent hereditary factors, or genes. These genes may meet in one individual, but they do not blend; when the germ cells of this individual ripen they will disjoin, segregate again without having had the slightest modifying influence upon each other.* The numerical ratios in which the hereditary characters reappear in later generations are a direct consequence of this segregation of the corresponding genes.

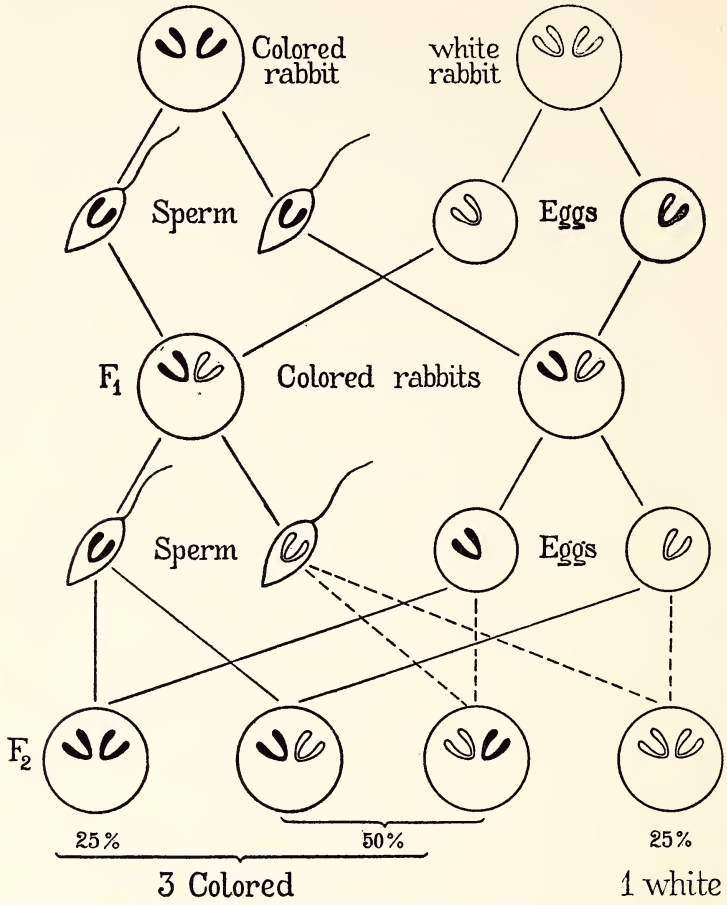
In Mendel's time even the fertilization process was unknown. We now know that the segregation and numerical distribution of the characters is an indispensable consequence of the law-governed distribution of the chromosomes which are the carriers of the hereditary units, the genes. The proof of this chromosome theory of heredity, which represents the sec-

ond fundamental advance in this science, we owe to T. H. Morgan and his co-workers, Bridges, Müller and Sturtevant.

Applied to our case the situation is as follows: the colored rabbit with which the experiment started has in both members of one particular chromosome pair a gene for dark pigmentation. Such chromosomes in the diagram, Text-fig. 8, are black. The white parent carries in each member of the corresponding chromosome pair an antagonistic, so-called *allelomorphic* gene which causes total lack of pigmentation. Such chromosomes are white in our diagram.

Since in the reduction division the chromosome number is reduced to half, each germ cell will receive only one representative of the respective chromosome pairs. At fertilization the offspring will accordingly receive one gene of each kind and be mixed, heterozygous, as regards genes for hair pigmentation.

Since these F_1 animals were all colored (see Text-fig. 7) the gene for color must be the more potent of the two, stamping the individual in spite of only being present in single dose. It is therefore said to be *dominant* in contrast to its opponent the white gene which behaves as a *recessive* gene, unable to manifest its presence when the gene for color and the gene for white are combined in one individual.



8. Chromosome diagram to explain the results of the crosses in Text-fig. 7. The chromosomes which carry the gene for color, solid (black), those carrying the white (albino) gene outlined (white) in the diagram.

But when the germ cells of these mixed, heterozygous F_1 individuals develop, then the two chromosomes again disjoin in the reduction division (see Text-fig. 8). Two kinds of germ cells are accordingly produced, and when these meet at random during fertilization, the following combinations of chromosomes result: black-black, black-white and white-white. But the chance of the combination black-white is twice that of any of the other combinations. We obtain in other words the combination black-black in 25%, black-white in 50% and white-white in 25% of the cases.

The F_2 offspring produced in this mating will accordingly be of three kinds: one quarter will carry the gene for color in double dose. They are pure, homozygous, for this gene, and will consequently be colored. Two quarters receive a gene of each kind. These animals, though mixed, heterozygous, will also be colored, since the gene for color is dominant over the white gene. One quarter, finally, will carry the weaker, recessive gene for white in double dose; they are homozygous for white. Here this gene can accordingly freely manifest its effect, and these animals will consequently be white. The final outcome expected is accordingly colored and white animals in the ratio $\frac{3}{4}$: $\frac{1}{4}$, exactly in conformity with the result of the actual experiment.

A glance at the diagram (Text-fig. 8) will also make us realize why the homozygous white rabbits when inbred give white offspring only. All the germ cells they produce will receive a chromosome carrying the white gene. The corresponding holds true for one of the three quarters of colored animals. These rabbits produce one kind of germ cells only, all with the gene for color. Hence, when inbred they give colored offspring only. But the remaining two quarters (in the middle) are genetically different. They are heterozygous, carrying one gene of each kind. Correspondingly, they produce *two* kinds of germ cells and therefore, when inbred, behave just like their parents giving colored and white offspring in the ratio 3 : 1. That heterozygous colored rabbits in matings to white rabbits will give colored and white animals in equal numbers is readily seen from the diagram, when we consider the kinds of germ cells they produce.

Accordingly in heredity we are confronted with an alternative: *an individual may carry a particular gene in double or in single dose, having received it from both parents or from one parent only.* No other possibilities exist. *The germ cells,* however, are genetically pure, they *will have any particular gene in single dose only.* This discovery which in its general form we owe to Mendel himself is, to quote Conklin, "one of

the greatest discoveries ever made in the field of biology, and it is as far reaching in results as it is simple in principle."

In order to become familiar with the terms homozygous—heterozygous, dominant—recessive, which are indispensable for any understanding of the hereditary phenomena, we may illustrate the law of segregation by aid of a popular example from human material. The brownish eye color is due to a dominant gene that induces the deposition of two pigment layers in the iris. The non-brown, i.e., bluish eyes have only one such pigment layer.

The gene for brown eye color (B) dominates over the gene for blue (non-brown) eye color (b). Blue eye color is accordingly a recessive character. Hence, all blue-eyed individuals must carry the gene b in double dose. They are homozygous (bb). The brown-eyed individuals, however, are of two kinds. Some are homozygous (BB), others are heterozygous only (Bb). Some brown-eyed individuals, namely, those which are homozygous (BB), will produce brown-eyed children only. All their children will receive the B gene and consequently be brown-eyed, since this gene is dominant.

But it is possible that two brown-eyed parents may produce some blue-eyed children. If both are hetero-

zygous (Bb), then half of their germ cells will contain the b gene. And if two such germ cells meet at fertilization, the result will be a blue-eyed child (bb). If, finally, a heterozygous brown-eyed individual (Bb) marries a blue-eyed individual (bb), we expect that half of the children will be brown-eyed (Bb), the other half blue-eyed (bb). The different combinations may readily be derived from the diagram Text-fig. 8 if we assume that the black chromosome carries the B gene, while the gene b is located in the white chromosome.

In order to relieve the minds of those who may encounter apparent exceptions to these rules, it may be added that in quite a few cases a rather detailed expert examination is required in order to settle whether the eye color belongs to the brown or the blue category. Other genes may also interfere and complicate the result. But, broadly speaking, the above holds true, and everybody may within his own acquaintance find examples which confirm the rules. It is particularly easy to ascertain how all the children have blue eyes, when both parents have pure blue eye color.

Dominant Inheritance of Human Defects

In man inbreeding is very rare. When an individual has a dominant anomaly the probability of an inter-

marriage with another similarly affected person is very remote. Practically all such affected individuals are therefore only heterozygous for the dominant gene and will accordingly produce two kinds of germ cells. In matings with unaffected individuals, homozygous for the corresponding normal gene, they give accordingly affected and normal offspring in the ratio 1 : 1.

A case from the author's own experience may serve as an illustration, that of a dominant, woolly and "self-bobbing" type of hair, very like that of the negro races, inherited in a Nordic strain through five generations. In Fig. 4, Plate I it is seen how a heterozygous woolly and short-haired woman in her marriage with a soft-haired husband produced three woolly and three soft-haired children, thus demonstrating the Mendelian segregation with text-book clarity.

Another simple dominant case we shall consider somewhat more in detail, since it illustrates different complications encountered in the studies of dominant pathological states in man. This involves a case of finger shortening, or *brachyphalangy* affecting the second phalanx of the second fingers and toes only (see Plate II, Figs. 5 and 6).

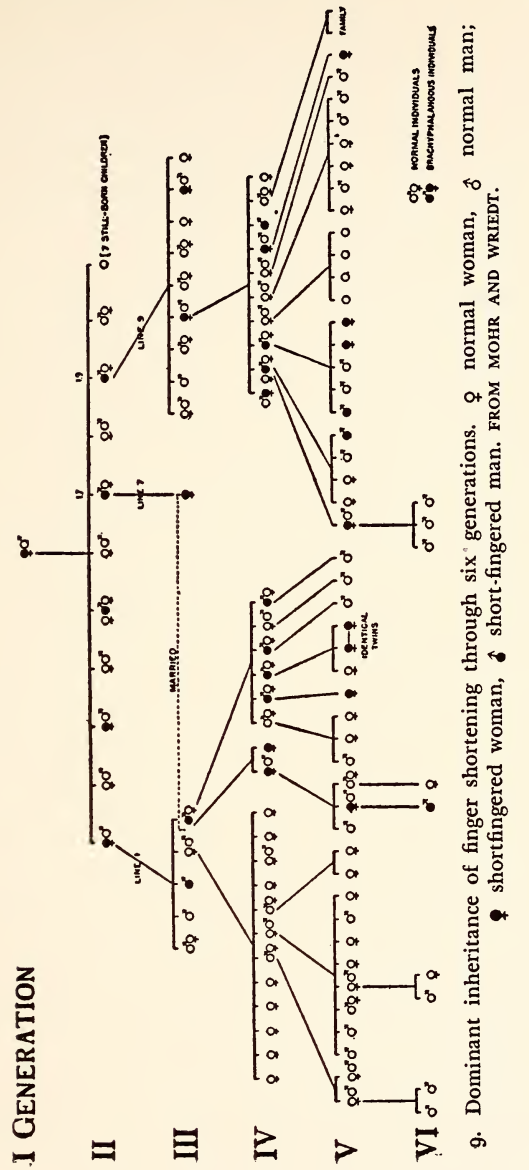
Thanks to an old family book, kept with admirable care, it was possible to trace its dominant inheritance six generations backwards to a Norwegian woman,

born in 1764. She gave birth to 10 living children—in addition to 7 stillborn ones—and, to quote the family book: "every second child had, as she has herself, a shortened or crooked fore-finger with one joint only."

A pedigree of this family which was studied by Wriedt and the author is presented in Text-fig. 9. Our photographs of the malformation cover five generations, our radiographs four. The pedigree illustrates how a dominant trait never skips a generation. If, conversely, a family member does not receive the dominant gene, then this individual as well as the descendants will be normal (see left part of pedigree Text-fig. 9).

Our material comprises 15 matings of heterozygous short-fingered by normal individuals. Among the resulting children 23 were normal, 26 short-fingered, in good accordance with the expected 1 : 1 ratio.

However, and this is the important point, this is only because we took the trouble of examining all the accessible family members, whether they were said to be normal or not. It then turned out that the malformation occurred in two types, one very pronounced and the other so weak that quite a few affected members believed themselves to be normal. There is reason to assume that the occurrence of two distinct types was in our case due to the action of an additional modify-



9. Dominant inheritance of finger shortening through six generations. ♀ normal woman, ♂ normal man; ♀ shortfingered woman, ♂ short-fingered man. FROM MOHR AND WRIEDT.

ing gene; such modifying genes which enhance or inhibit the effect of another gene being relatively common. In one woman the radiographs even showed phalanges of normal length, in spite of the fact that by her offspring she was proved to carry the dominant gene in heterozygous condition.

This gives us an opportunity of emphasizing that the rule for dominant genes as "not skipping a generation" is far too dogmatic. *Some dominant genes are so constant in their manifestation that they always strike through. But a great many are very variable in their somatic effect so that numerous heterozygous individuals may be perfectly normal.* This applies, as we shall see, to a great number of hereditary pathological states in man.

Moreover, the text-book presentation of ideal cases has led to the wrong conception that if we know the action of a dominant gene when heterozygous, we may conclude that it will have the same effect when homozygous, i.e., in double dose. That this does not hold true may be illustrated by a first cousin marriage of two heterozygous family members in the third generation of the pedigree in Text-fig. 9. This marriage gave rise to two daughters, one short-fingered of the ordinary type, the other a cripple without fingers and toes and "with the entire osseous system in disorder."

Only with great care was this cripple kept alive for one year.

A large number of parallels from experimental material justifies the assumption that this cripple had received the gene for finger-shortening in double dose. *A dominant gene which when heterozygous causes only trifling malformations may, in other words, in homozygous condition cause far more pronounced, and eventually deleterious character changes.*

The practical bearing of this knowledge is obvious. As doctors we must advise against intermarriage among persons who exhibit one and the same, even harmless dominant malformation. And since numerous dominant genes are so variable in their effect that heterozygous individuals may be perfectly normal, I think it desirable to advise against intermarriage in general within families in which dominant malformations occur. That intermarriage in itself is not harmful, will be shown later (p. 205).

A striking illustration of the variability of dominant malformations in heterozygous individuals is afforded by the *syndactyly* case of Scott presented in Fig. 7, Plate II. Most affected individuals show a simple webbing only, and one heterozygous individual in this family also had normal hands and feet. But in quite a few, gross lobster-claw malformations were present.

An analogous variability is found among the very numerous cases of dominant *polydactyly,* studied by Sverdup-Sömme, and others, where one hand may be normal while the other has one or more supernumerary fingers.

That simple dominant genes may cause very shocking malformations may be seen from the mother and child with "split" hands and feet presented in Fig. 8, Plate II, or from the Brazilian case reproduced in Fig. 9, Plate III. Everybody will probably agree that sterilization of the affected individuals who are certain to transmit this terrible malformation to half of their children, is here strongly indicated.

Finally, as a curiosity among these scattered illustrations derived from the hundreds of cases of dominant malformations of hands and feet in man, may be mentioned a case of hereditary finger-shortening utilized in legal medicine in Norway.

The mother of an illegitimate child called attention to the fact that both the child and the alleged father had abnormally shortened fingers. The latter, of course, denied the parenthood, as they always do. By appropriate examination it was found that while the mother had perfectly normal hands, both the man and the child showed a pronounced brachyphalangy, affecting, as is frequently the case, the second row of

phalanges (the last one to ossify), in an elective way (see Figs. 10 and 11, Plate III).

When it could be shown that the mother's family as well as other persons in the rural district concerned did not exhibit analogous malformations, it could, in view of our extensive knowledge of these cases, be concluded that the mother's assertion was in all probability correct. And the man was found guilty.

As will be understood, this man was heterozygous only, and the chances were even for his begetting a normal child. But he happened to draw the wrong card and stamped his own child.

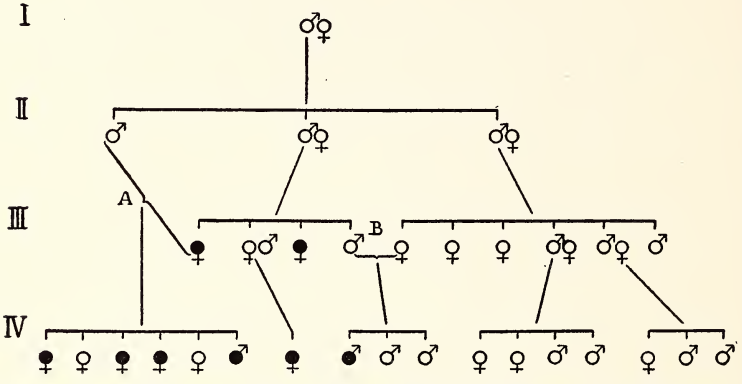
Recessive Inheritance of Human Abnormalities

Turning now to the recessive genes, these have no visible effect whatever in heterozygous conditions, i.e., when present in single dose only. They may therefore pass undetected through an unlimited number of generations. Only if two such heterozygous individuals happen to mate, the corresponding character may come to light quite unexpectedly in some of the children. Hence, *consanguineous marriages favor the appearance of recessive traits.*

Universal *albinism,* in which an almost complete lack of pigmentation of skin, hair and eyes is combined with a reduction of the retinal nerve fiber layer

and the elements of the macula lutea, the most light-sensitive spot in our retina, may serve as a classical illustration. The eye alteration accounts for the reduced seeing power and tendency to nystagmus, a peculiar type of reflectory spasms in the eye muscles.

The pedigree data on albinism which are now very extensive all exhibit a high degree of consanguinity



10. Pedigree illustrating recessive inheritance of albinism. In the middle, marriage of heterozygous first cousins. To the left, marriage of heterozygous uncle with albinotic niece ("back-cross"). The affected individuals denoted by solid symbols. AFTER TERTSCH.

among the producers of albinotic children. Consanguinity is about 50% in Langsley's, and about 33% in Davenport's material. The consanguinity is well illustrated by the pedigree of Tertsch, Text-fig. 10.

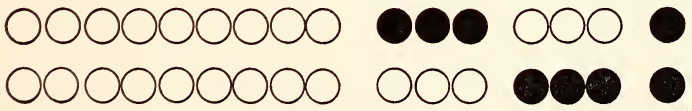
A family with albinotic children is presented in Fig. 12, Plate III. As seen from the picture both parents are

perfectly normal. That they nevertheless carry the recessive gene is evidenced by their offspring.

This fundamental relation, that a strictly hereditary anomaly may be transmitted through perfectly normal individuals has been the cause of much misunderstanding. And still many people stick to the entirely wrong conception that only those anomalies are hereditary which manifest themselves *both* in parents and offspring. Nothing could be more erroneous.

Theoretically we expect in a mating of two heterozygous individuals 25% of the offspring to be albinotic, as seen from the diagram involving albinism in rabbits, Text-fig. 7, p. 49. But in human material with the small average number of children, many such matings will, by this 3 : 1 probability, give *no* affected children and consequently escape detection.

Thus, among 16 two-child families with heterozygous parents 9 families are expected to consist of two normal children, 6 to comprise one normal and one albinotic child, while in only 1 family both children are expected to be albinotic. As seen from the symbols below,



we obtain by adding all these children 24 normal and 8 albinos, i.e., normal and albinotic children in the expected ratio 3 : 1. Hence, by counting the offspring only in those families where albinotic children occur,—the seven sets to the right,—the percentage of affected children will be far in excess of expectation.

This source of error is eliminated by special statistical methods elaborated by Weinberg, Lenz, Haldane, Hogben, and others. To give an idea of the principle of such methods the following may suffice: we have seen how, by counting the children in families where albinotic children occur, we obtain a selected material including too many albinos in comparison with the normals. But the *siblings* of each albinotic child are subject to the same probability as the affected individuals, and this material of *siblings* is not selected. The calculation may accordingly be based on these.

For albinism Hogben after a critical sifting of 600 pedigrees collected by Pearson, Nettleship and Usher and statistical treatment of this material arrives at a percentage of 29, a result that is somewhat above expectation. The latter deviation may be accounted for by another source of error, the "Interessantheitsauslese" of the Germans: families with an exceptionally high number of affected children are particularly likely to attract attention and to be recorded.

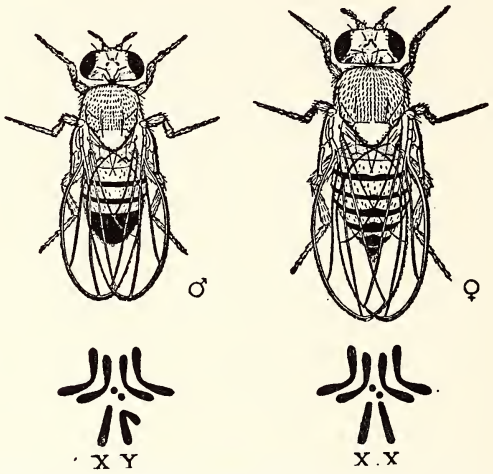
This may suffice to give an idea of some of the difficulties encountered in dealing with recessive characters in man. That albinism here, as in a series of other mammals, is a clear-cut recessive is also confirmed by the crucial test that when both parents are albinotic the same is true of all their children.

2. SEX-LINKED INHERITANCE. ILLUSTRATIVE CASES FROM MEDICINE

If from these illustrations of monofactorial inheritance of pathological states we now return to the chromosome mechanism, the following question arises: granted that the inheritance of the contrasting characters, normal—abnormal, agrees with the distribution of the chromosomes in which the respective antagonistic, or allelomorphic genes are supposed to be located. But what about the sex chromosomes? If the X-chromosome is also a carrier of genes, then the corresponding characters must be expected to show a very different type of inheritance, since this chromosome is simplex in males and duplex only in the females (cf. p. 39).

Let us answer this question by aid of the classical experiment of T. H. Morgan, which represents the starting point of the Drosophila work, that has given us an undreamt-of insight into the internal architecture of the germinal material.

For his experiments Dr. Morgan used a tiny little fly, the vinegar fly, *Drosophila melanogaster,* of grayish body color and with brilliantly red compound eyes. This animal seems especially created for experimental purposes. It produces a new generation every twelve days all the year round, each female giving an offspring of 300-400 individuals, and the distinction between



11. The vinegar fly, Drosophila melanogaster, male (♂) and female (♀). Below, the male and female chromosome groups. Note two rod-shaped X-chromosomes in the female, a rod-shaped X- and a hook-shaped Y-chromosome in the male body cells. FROM MORGAN.

males and females is very easy thanks to the different abdominal coloring and the sex combs which are present on the forelegs of the males only (see Text-fig. 11).

Above all, the main advantage is that this fly has

only 8, i.e., four pairs of chromosomes, comprising two rod-shaped X-chromosomes in the female, a rod-shaped X- and a hook-shaped Y-chromosome in the male (Text-fig. 11).

In May, 1910, Morgan found in his cultures a single male fly which had white eyes! When mated to a normal red-eyed female this exceptional male gave red-eyed offspring only (Text-fig. 12). But, when as a next step these F_1 flies were inbred, the white eye color reappeared in the next generation, though only in half of the sons, never in the daughters! However, when one of the normal F_1 daughters was back-crossed to her white-eyed father, both red-eyed and white-eyed sons and daughters appeared, and in the definite ratio 1:1:1:1. Moreover, if one of these white-eyed females is mated to a wild-type, red-eyed male, all the sons have white eyes, all the daughters red (see Text-fig. 13).

The explanation of this remarkable criss-cross inheritance is as follows:

The white-eyed male carries in its single X-chromosome (white in the diagram) a recessive gene for white eye color. The Y-chromosome is virtually empty of ordinary genes, for which reason the recessive white gene manifests its action in spite of the presence of a Y-chromosome. His daughters receive the white X, but in addition an X with the dominant normal allelomorph

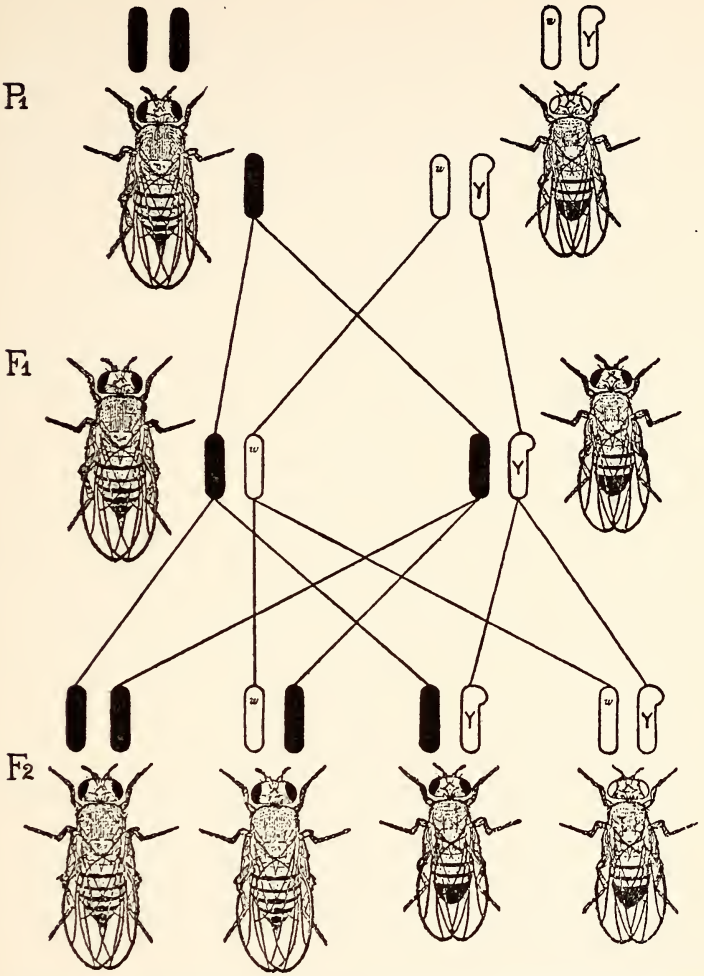
for the contrasting red-eye color from their mother. They will accordingly be red-eyed. The same is true of the sons, since these receive a wild-type X-chromosome from their mother (see Text-fig. 12).

If now these F_1 daughters are mated to their own brothers, half of their sons receive the white X; and since the Y-chromosome which they in addition receive from their father has no antagonistic effect, they will be white-eyed like their grandfather.

A female in order to be white-eyed must carry the recessive gene in both members of the X-chromosome pair, and such a homozygous white-eyed female when mated to a red male gives white sons only, since the males always get their single X from their mother (see Text-fig. 13).

The discovery of this so-called *sex-linked inheritance* immediately gave the clew to some very puzzling cases from human pathology, such as *hæmophilia,* a certain type of *night-blindness with myopy,* Leber's type of *optic atrophy,* Gower's *pseudo-hypertrophic muscular paralysis,* as well as ordinary *color blindness.*

Thus, it had long been known of color blindness, for instance, that it affects males in an elective way, and that normal females serve as *carriers,* transmitting the anomaly to some of their sons. The old empirical rule of the clinicians states that sons of women whose fathers



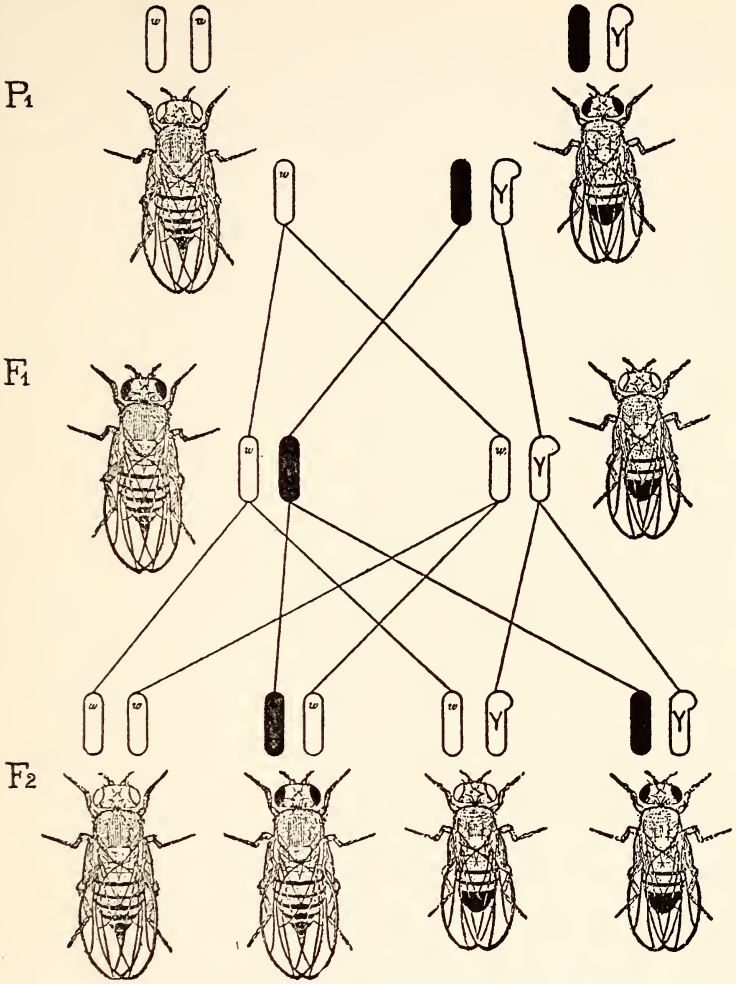
12. Sex-linked inheritance. Cross of a red-eyed Drosophila female with a white-eyed male. The X-chromosome carrying the recessive gene for white eye-color (w), outlined (white) in the diagram, those which carry the alternative gene for red eye color, solid (black). X-chromosome rod-shaped, Y-chromosome hook-shaped. FROM MORGAN.

were color-blind are most likely to be color-blind. Color-blind individuals are not blind with respect to color vision, as the designation might suggest. They simply lack the ability to distinguish red and green colors, they are *"red-green blind."* They are, for instance, bad strawberry-pickers.

The explanation is as follows (see Text-fig. 14):

The color-blind man carries in his single X-chromosome a recessive gene for color blindness. The genetically empty Y-chromosome does not prevent its manifestation, and is omitted in the diagram. His daughters receive the affected X, but in addition a normal X with the contrasting dominant gene for normal color vision from their mother. They are consequently themselves normal. The sons are also normal, since they receive a normal X-chromosome from their mother (see Text-fig. 14, 1).

But if such a heterozygous woman carrier gives offspring with a normal man, then half of her sons will receive the abnormal X and be color-blind (see Text-fig. 14, 2). If, as occasionally happens, a heterozygous woman gives offspring with a color-blind man, then half of her daughters will receive the recessive gene for color blindness in double dose and be color-blind. And such homozygous color-blind women will produce color-blind sons only, since the sons always receive



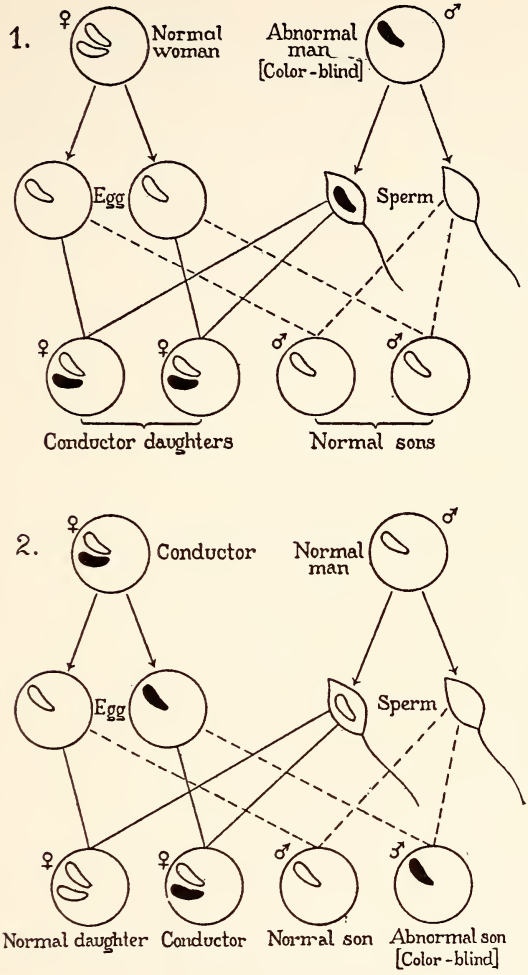
13. Cross between a white-eyed Drosophila female and a red-eyed male. All the daughters red-eyed, all the sons white-eyed. When these F_1 flies are inbred, red-eyed and white-eyed sons and daughters are obtained in the ratio 1 : 1 : 1 : 1. FROM MORGAN.

their X-chromosome from the mother. Mass statistics indicate a frequency of 8% of color-blind men and 0.5% of color-blind women in the general population. To special aspects of the color blindness problem we shall return later (p. 129).

As regards *hæmophilia,* more than 200 pedigrees demonstrate the sex-linked inheritance with perfect clearness (see Text-fig. 15). The disease is characterized by the failure of the blood to clot in the normal way, so that even superficial lesions, the extraction of a tooth, a slight cut in the skin, etc., may lead to dangerous, frequently even fatal bleeding.

One special point needs particular comment here, viz., the fact that no conclusive cases of true hæmophilia are known in women. Bucura, who examined critically the known cases of alleged hæmophilia in women, found that every single one out of 197 assumed cases had to be excluded. Schloessmann was able to demonstrate that in his large material from Württemberg quite a few women family members, who had passed through periods of rather severe bleeding, were heterozygous only.

Schloessmann also made the interesting observation that the blood of these heterozygous women had a prolonged clotting time, a fact which indicates that the sex-linked gene for hæmophilia is not completely re-

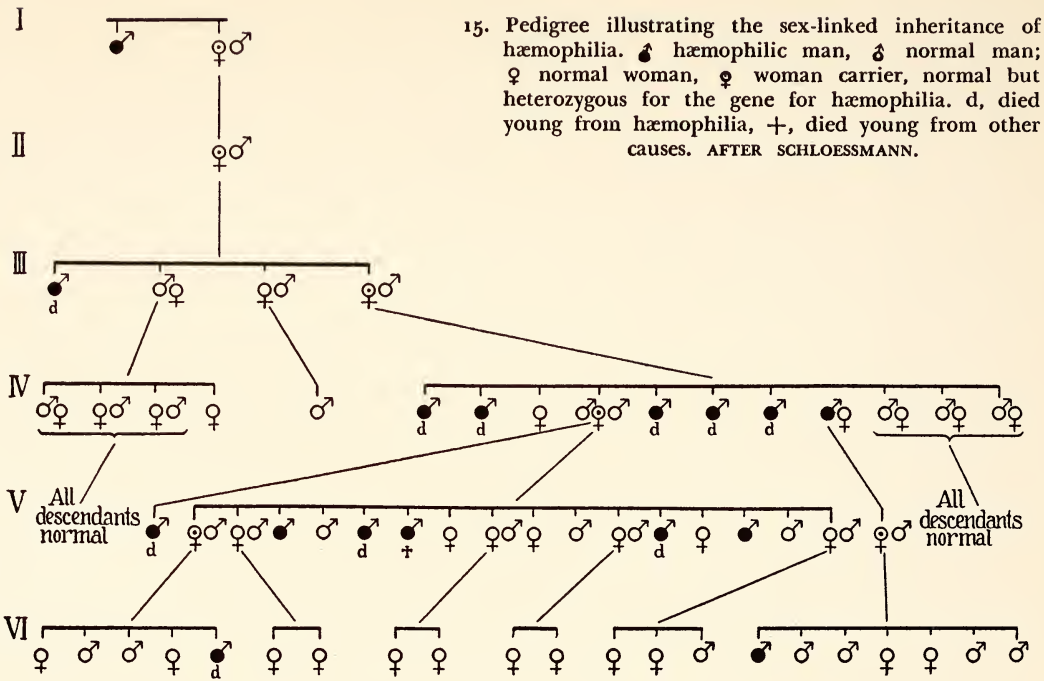


14. Diagram to illustrate the sex-linked inheritance of color-blindness in man. The X-chromosome carrying the recessive gene for color-blindness solid (black) in the diagram, the X-chromosome carrying the alternative dominant gene for normal color vision, outlined (white). The Y-chromosome disregarded in the diagram.

cessive. Davidson and MacQuarry made the same observation in the United States, while Weinberg and also Thomsen failed to find a similar delay. Possibly other genetic or environmental factors may influence the result.

However this may be, the fact remains that no homozygous women bleeders have yet been found. The requirement for the occurrence of a homozygous woman bleeder is, as will be understood from what has been said, a marriage between a heterozygous woman and a bleeder. Such cases are necessarily rare, since so many hæmophilic men die early without leaving offspring (see Text-fig. 15). But some such marriages of carrier with bleeder are found in the literature. Weinberg and Bauer have therefore advanced the hypothesis that the gene for hæmophilia, when present in double dose in women, causes deleterious changes which lead to death already *in utero,* before birth.

As we shall see later there are many parallels for such a situation from experimental genetics (cf. p. 139). But in the case of hæmophilia the question can hardly as yet be regarded as settled. Recently Birch presented evidence to the effect that the ovarian secretions counteract hæmophilia in women, and that in agreement with this ovarian extracts have a favorable effect against this disease in male bleeders. If this is



15. Pedigree illustrating the sex-linked inheritance of hæmophilia. ♂ hæmophilic man, ♂ normal man; ♀ normal woman, ♀ woman carrier, normal but heterozygous for the gene for hæmophilia. d, died young from hæmophilia, +, died young from other causes. AFTER SCHLOESSMANN.

the case, the gene for hæmophilia in addition to being *sex-linked,* i.e., located in the X-chromosome, is also *sex-limited* in its effect, which means more pronounced in its effect in one sex—here one hormone environment —than in the other.

In passing it may be mentioned that Klug on re-examining the most famous hæmophilia pedigree, the Mampel family of Lossen, found that the recorded number of 37 affected was too high by no less than 14 individuals. The latter had declared that they were bleeders in order to escape military service—a striking illustration of the sources of error encountered in human material. As a general rule the reliability of the data is here inversely proportional to their remoteness in time. And when it is a question of abnormalities, malformations, etc., even intentionally wrong information cannot always be excluded.

But animals cannot tell fibs. And they can be used in experiments where man cannot. The only accessible way for progress in human genetics is an indirect one. The general laws of heredity must be unveiled by investigations with experimental material, plants and animals, and the interpretation of the carefully collected data on hereditary characters in man must in every case rest upon the comparison with analogous

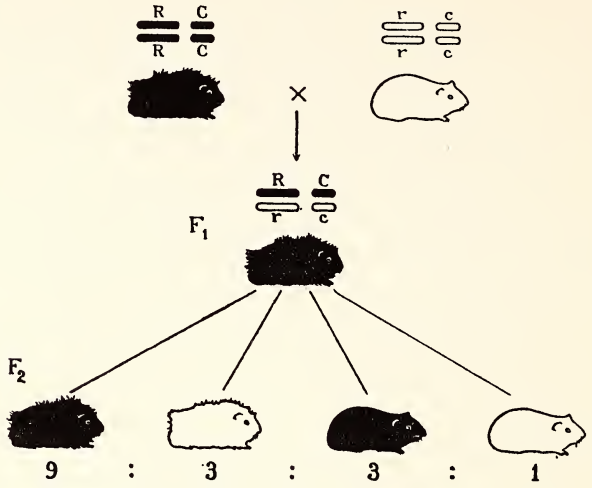
evidence from experimental genetics. There is no hope of detecting new genetic principles in human material.

3. MENDELIAN INHERITANCE INVOLVING MORE THAN ONE FACTOR PAIR

We have seen that the inheritance of monofactorial cases, sex-linked as well as autosomal, is fully in accordance with the chromosome theory of heredity. But what about cases in which the two individuals that are crossed differ, not in one, but in *two* pairs of contrasting characters?

This question may be answered by aid of the following example. If we mate a guinea-pig with rough coat and colored fur, with one that has smooth coat and white (albino) fur, the offspring (F_1) are all rough and colored. But if we inbreed these rough and colored animals we obtain in the next generation (F_2) four different classes (of which two are new), viz.: rough colored, rough white, smooth colored and smooth white. And if we add together the offspring obtained in a sufficient number of such matings it is found that these classes appear in a definite numerical ratio, viz., 9 : 3 : 3 : 1 (Text-fig. 16). Only in one out of each 16 cases do we obtain animals that are both smooth and white like one of the grandparents. This result is paral-

lel to those obtained by Mendel himself in analogous experiments with plants.



16. Cross between a rough-coated colored guinea-pig and a smooth white (albino) guinea-pig. The two chromosome pairs involved differently marked in the diagram. Dominant genes indicated by capital letters (R = rough, C = colored), recessive genes by small letters (r = smooth, c = white). In the second generation (F_2) four different classes are obtained in the ratio 9 : 3 : 3 : 1.

On the chromosome theory the explanation is simple enough. Since all the F_1 animals were rough and colored, the genes for these characters (R and C) must be dominant. The genes for the contrasting characters (r and c) must be recessive. The rough colored animal with which the experiment started carried in both members of one chromosome pair the gene R, in both members of another chromosome pair the gene C. Its

mate, the smooth white animal, carried in both members of the corresponding chromosome pairs the antagonistic recessive genes r and c.

These two animals had in other words the following chromosome combinations $\frac{R\ C}{R\ C}$, and $\frac{r\ c}{r\ c}$ respectively. Their germ cells will only receive one set of chromosomes, viz., R C and r c. Hence, the F_1 animals which result from the union of these germ cells will be of the constitution $\frac{R\ C}{r\ c}$, they carry four different genes. When the chromosomes in which these genes are located disjoin in the reduction division, four different kinds of germ cells are produced, viz., R C, R c, r C and r c. At fertilization, the union of one egg cell with one sperm, $4 \times 4 = 16$ possibilities of combinations accordingly exist:

		Eggs			
		R C	R c	r C	r c
Sperm	R C	R C ■ R C	R c ■ R C	r C ■ R C	r c ■ R C
	R c	R C ■ R c	R c □ R c	r C ■ R c	r c □ R c
	r C	R C ■ r C	R c ■ r C	r C ● r C	r c ● r C
	r c	R C ■ r c	R c □ r c	r C ● r c	r c ○ r c

If we now add these classes, remembering that the dominant characters rough and colored will appear also when the corresponding genes R and C are present in single dose (heterozygous condition), while the recessive characters only appear in individuals which carry the genes r and c in double dose (homozygous condition), it is readily seen that we expect the following classes: 9 rough colored ■, 3 rough white □, 3 smooth colored ●, and 1 smooth white ○, in full conformity with the result of actual experiments.

If instead of raising an F_2 generation we had back-crossed the heterozygous F_1 rough colored guinea-pigs to a homozygous smooth white guinea-pig, we would have obtained the same classes as above, but in the ratio 1 : 1 : 1 : 1. The F_1 rough colored animals will produce four classes of germ cells in equal numbers. But the homozygous smooth white animal will give one kind of germ cell only, all with one representative of the r-carrying and one representative of the c-carrying chromosome. Such an experiment, a *back-cross* to the homozygous recessive type, is particularly revealing, and therefore most favorable when it is a question of testing what kinds of germ cells an F_1 individual produces.

In human material cases involving more than one pair of characters would generally be very hard to

clear up from pedigree studies. But the above simple experiment involving the raising of an F_2 generation when two pairs of contrasted characters are involved makes us acquainted with one of the basic causes of *genetic variability*. In this experiment only two pairs of chromosomes differed, each in one pair of genes. If in a human being the members of all the 24 pairs of human chromosomes differed correspondingly with respect to one pair of genes only, more than 16 million different germ cells would be produced. No wonder that with one exception (identical twins) two individuals are never like each other.

The cause of this rich variety of gene combinations in the germ cells is the random distribution of the gene carriers, the chromosomes, in the reduction division where the two members of each pair disjoin and enter opposite daughter cells.

Let us visualize what actually happens in the reduction division in a case involving only three pairs of chromosomes, the members of which differ with respect to one gene. These pairs may be represented by playing cards; the Ace of hearts and of spades representing one pair, the King of hearts and of spades the second, and the Queen of hearts and of spades the third.

Place the three hearts in one consecutive series, and

the three spades in a corresponding series below, opposite to the former, thus, ♥A ♥ K♥Q / ♠A ♠ K♠Q. If we now imitate the reduction division by pulling the two series apart, then the resulting single series will comprise only hearts and only spades respectively.

But the pairs may be arranged otherwise. We may, for instance, place the Ace of spades and the King and Queen of hearts in one series, ♠A ♥ K♥Q / ♥A ♠ K♠Q . Then the opposite series will comprise the Ace of hearts and the King and Queen of spades. The two single series resulting from a "reduction division" will in this case differ from those obtained above.

If we test all the existing possibilities we will find that there are four possible different arrangements of the pairs of cards when in each case cards of similar value are placed opposite to each other. This gives in all eight different kinds of single series. The single series of cards corresponds to the single series of chromosomes typical of the germ cells. In a case involving three pairs of chromosomes, the members of which differ with respect to one gene, eight different kinds of germ cells are produced.

By mating two individuals each of which produce eight different kinds of germ cells we obtain $8 \times 8 = 64$ different kinds of fertilized egg cells, *zygotes*. When we

remember that of the two allelomorphic genes present in each chromosome pair one gene is dominant in relation to its opponent, it is easy enough, by aid of the checker board method (p. 81), to see that we obtain in this case eight different kinds of character combinations in the ratio 27 : 9 : 9 : 9 : 3 : 3 : 3 : 1, fully in accordance with Mendel's own results from experiments involving three pairs of characters.

4. LINKAGE GROUPS OF GENES

We have so far considered cases, the inheritance relations of which could be consistently explained on the assumption that the gene involved is carried by a particular chromosome.

However, in man we already know many scores of hereditary characters; and in Drosophila with its four pairs of chromosomes several hundreds of hereditary characters, affecting every part of the fly, have been discovered. It is then a simple logical inference that *each chromosome must contain not one, but many genes.* And if this is the case, we must expect that genes which are located in *one and the same* chromosome will not show free Mendelian segregation, but tend to keep together in inheritance.

In full accordance with this expectation Morgan and his co-workers were able to demonstrate that all the

known hereditary characters in the vinegar fly fall in four different linkage groups, corresponding to the four chromosome pairs typical of this species. Members belonging to one and the same group *show linkage, have a tendency to keep together in inheritance,* while characters which belong to different groups show free Mendelian segregation.

Moreover, the *size* of these groups of linked genes corresponds strikingly to the actual size of the four chromosomes present in each of the two homologous series in Drosophila (cf. Text-fig. 11, p. 68). Thus, there is one large group comprising more than a hundred genes, all of which show sex-linked inheritance, since they are located in the rod-shaped X-chromosome. Two still larger groups correspond in number to the size of the two large V-shaped autosomes, the so-called II and III chromosomes. Finally, corresponding to the small size of the tiny, round, so-called IV chromosome, there is a small group which in striking contrast to the others comprises a few genes only.

The discovery of this general law, that *the number of linkage groups corresponds to the number of chromosome pairs,* is one of the outstanding achievements of the Drosophila work. Similar linkage groups have since been discovered in a steadily increasing number of plants and animals. In man all those genes

which show sex-linked inheritance represent one such linkage group (cf. p. 124).

How the linked genes, genes which are located in the same chromosome, behave in inheritance will be dealt with later (p. 106).

5. PROOF OF THE CHROMOSOME THEORY OF HEREDITY. SEX MOSAICS AND OTHER ABERRATIONS

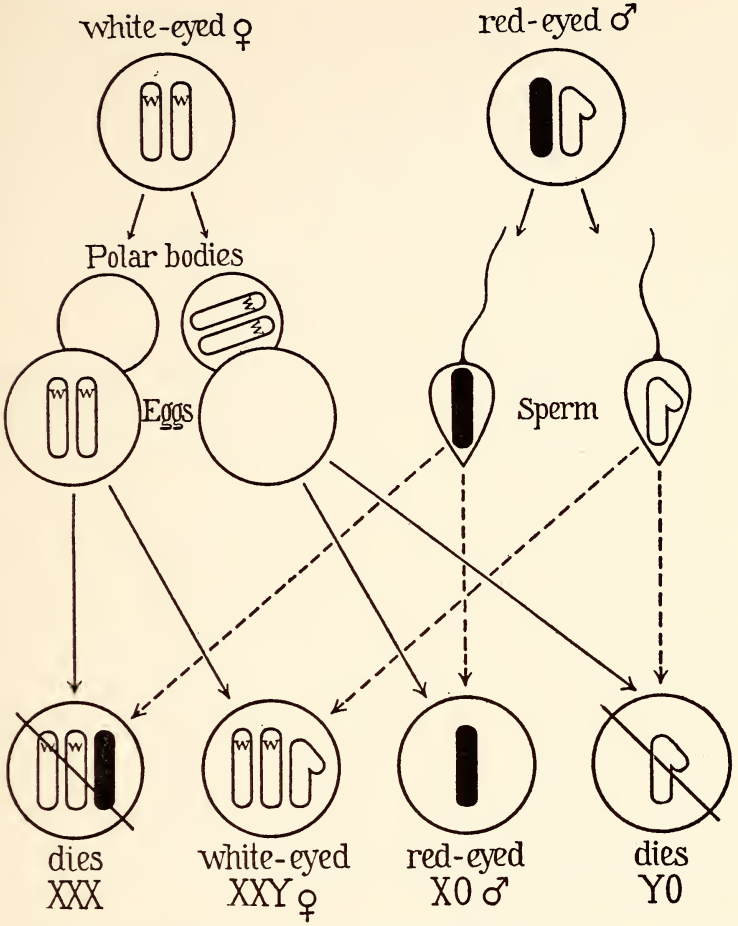
ALL the discussed facts, though extremely suggestive, have only the character of circumstantial evidence in favor of the chromosome theory of heredity. The credit of having delivered the final, conclusive proof we owe to C. B. Bridges, then a young student at Columbia University.

We remember how a female, homozygous for the sex-linked recessive white eye color, when mated to a normal red-eyed male will give red-eyed daughters and white-eyed sons. Very rarely, however, it happens that an exceptional *white-eyed* daughter or a *red-eyed* son appears in this cross. Bridges, following Bateson's slogan: "Treasure your exceptions!" tested these individuals and found that, while the exceptional males were sterile, the white daughters were fertile and continued to give exceptions to normal sex-linked inheritance in later generations. An ingenious genetical analysis of the case led to the following result:

It sometimes happens that the two X-chromosomes of a female by accident fail to disjoin in the reduction division, so that either 2 X eggs or no X eggs are formed (Text-fig. 17). If these are fertilized by normal X or Y sperms, the following chromosome combinations result: XXX, XXY, XO and YO.

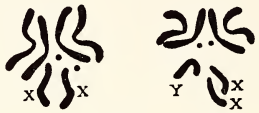
The XXX individuals show gross abnormalities and usually perish, and so always do the YO zygotes. The XO individuals are sterile, but normal-looking red-eyed males,—red-eyed since they have received a wild-type X from their red-eyed father, and males since they have only one X-chromosome. That they are sterile is due to the lack of a Y-chromosome, a fact which demonstrates that the Y must have an action that is indispensable for the fertility of the males. Finally, the exceptional XXY individuals are fertile, white-eyed females,—females since they have two X's and white-eyed since the empty Y-chromosome does not prevent the manifestation of the two white genes which they have received from their mother.

The cause of all these aberrant types is the *non-disjunction* of the X-chromosomes in the mother. From his genetical analysis, Bridges was able to pick out the secondary exceptions among the offspring of the XXY females and predict that they had an X or a Y-chromosome in excess, i.e., nine instead of the ordinary eight



17. Diagram to illustrate non-disjunction of the X-chromosomes during the egg-cell development of a homozygous white-eyed Drosophila female, and the progeny resulting when XX and O eggs are fertilized by normal sperms from a red-eyed male. The X-chromosomes carrying the recessive white gene (w) in outline; the X-chromosome carrying the dominant gene for red eye color, in solid black. The Y-chromosome hook-shaped. AFTER BRIDGES.

chromosomes. The microscopical examination of their cells fully confirmed his prediction (cf. Text-fig. 18 and Fig. 13, Plate IV). This is a conclusive proof of the chromosome theory of heredity, quite on a level with any scientific proof whatever.



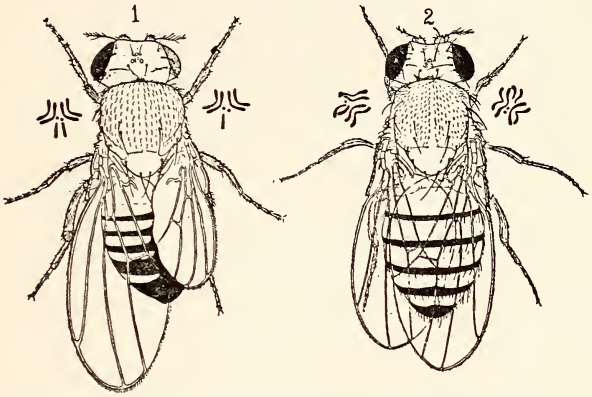
18. To the left the chromosomes in a cell from a normal Drosophila female; two rod-shaped X-chromosomes. To the right the chromosomes in a cell from an exceptional XXY female; two rod-shaped X-chromosomes and an extra hook-shaped Y-chromosome. FROM BRIDGES.

This combined genetical and microscopical proof has since been extended to a large series of other chromosome aberrations, such as non-disjunction of the small, IVth chromosome, or elimination of a particular chromosome in somatic cells during development, only to mention a few.

The study of chromosome aberrations now represents a very important field of animal and plant genetics, and evidence derived from these studies has important bearing on the questions of heredity and disease. While balanced types of chromosome aberrations, as for instance the addition of one or more full sets of chromosomes, frequently lead to luxuriant growth, as in many of our garden plants, unbalanced

types, as for instance loss or excess of one particular chromosome or of a chromosome section may induce gross abnormalities, sterility or non-viability.

In this connection let us briefly consider a few special cases of deviations from the normal chromosome



19. 1, Drosophila sex mosaic (gynandromorph). Left half female of the wild type: red eye color, long wing. Right half male with eosin eye color and miniature wing. AFTER MORGAN AND BRIDGES. 2, A somatic mosaic female, left half with minute bristles and shortened, bluntly rounded wing; right half normal bristles and normal wing. FROM MOHR. For explanation see text.

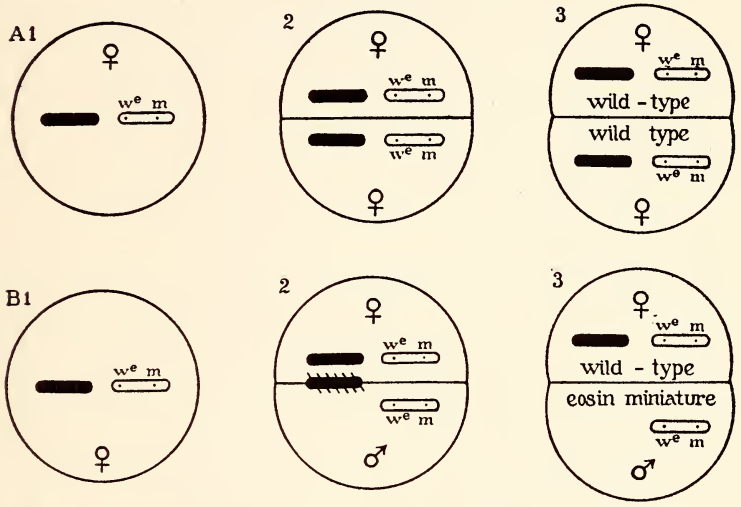
make-up, that are of importance for our understanding of particular pathological phenomena to be dealt with later.

Every now and then it happens in insects, birds and other forms, that individuals occur which are *sex mosaics,* female on one side, male on the other, so-called *gynandromorphs.* In Text-fig. 19, 1, is presented

such a gynandromorph from Drosophila. The left part is female and wild-type (red-eyed, long-winged, female abdominal coloring), while the right part is male (smaller size, sex comb on foreleg, male abdominal coloring). In addition, the male part exhibits two well-known recessive hereditary characters, viz., eosin eye color and miniature wing.

The explanation is as follows: This gynandromorph is derived from a mating of a wild-type female with an eosin miniature male, and we would expect that the fertilized egg would develop into an ordinary wild-type female. It has received a wild-type X-chromosome from the mother and an X-chromosome with the recessive genes eosin and miniature from the father. When the egg cell divides the chromosomes are split lengthwise, and the two daughter-X's formed enter opposite daughter cells (Text-fig. 20, A 2-3). These cells, as well as all their daughter cells again, will accordingly be female, since they have two X's, and wild-type, since they are only heterozygous for the two recessive genes. But occasionally it happens—and this is what has occurred in the present case—that one of the two daughter-X's that was formed in the cleavage division, is lost by accident, probably by being caught in the cleavage constriction (Text-fig. 20, B2). In the present case it is the wild-type daughter-X

that has been eliminated. Hence, only one of the resulting daughter cells will be 2X and female, while the other will receive one X only, and consequently be male (Text-fig. 20, B_3). Moreover, the male part which is derived from this cell by ordinary cell divi-



20. Diagram to explain the origin of the gynandromorph in Text-fig. 19, 1. A1-3, normal distribution of the daughter X-chromosomes in the first division of the fertilized egg. One X-chromosome (outlined) carries the recessive genes for eosin eye color (we) and miniature wing (m); the other wild-type X-chromosome in solid black. B1-3, elimination of one wild-type daughter X resulting in gynandromorphism.

sions will show the characters eosin and miniature, since no additional X is present which may prevent the recessive genes from manifesting their effect.

The fundamental conclusion to be derived from these cases, which were first cleared up by Morgan and

Bridges, is the fact that *each particular cell is self-determining, i.e., the somatic characters of each cell are a direct expression of its own chromosome and gene equipment.* If a chromosome is lost in a body cell, the somatic alteration induced will in other words be restricted to a limited region of the individual, to that part which is derived from the cell in question. As one of the causes of *mosaicism* this evidence is of interest for our later discussion of the tumor problem.

In Text-fig. 19, 2, is presented another case of mosaicism, a female the left half of which has very tiny and slender hairs and bristles and a shortened, bluntly rounded wing, while the right half is perfectly normal. The character changes present on the left side are due to the fact that one of the two small autosomes belonging to the so-called IVth chromosome pair has been lost in the first division of the fertilized egg. Those cells which constitute the left half of the mosaic female have received only one representative of this pair, for which reason this part of the individual exhibits the character changes mentioned (see Plate IV, Fig. 13).

Somatic chromosome aberrations of the last mentioned type—also denoted as somatic "chromosome mutations"—may possibly offer an explanation of some of the cases of congenital unilateral character changes in man. In Plate IV, Fig. 14, is presented as an illustra-

tion a case of *congenital hemi-hypertrophy* in which the entire left body half is distinctly larger than the right half. Quite a few such cases are recorded in the literature; in many of these the skin on the hypertrophic side shows a tendency to development of pigmented nævi (moles).

If the loss of a particular chromosome occurs during the later embryonic development, then only a limited part of the individual will have an atypical chromosome complement, a situation that accounts for the appearance of a smaller mosaic area, even a mere patch with atypical characters, surrounded by normal tissue (see in this connection also p. 200).

That special cases of chromosome aberrations may throw light on abnormal inheritance in man is illustrated by the following example: Mrs. L. V. Morgan has discovered a particular stock in which females, homozygous for the sex-linked recessive yellow body color, in matings to normal gray brothers, quite contrary to expectation, transmit the yellow body color to all their *daughters,* while all the sons are gray like the father.

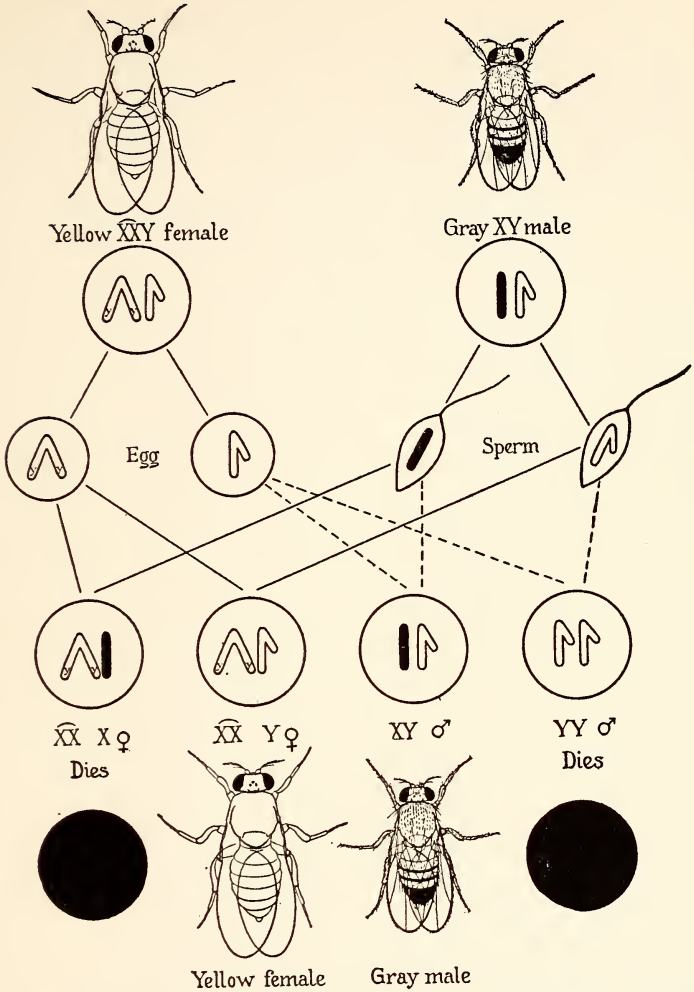
Combined genetic and microscopic tests proved that the yellow females were XXY, and that the two yellow-carrying X's had become permanently attached, forming a V-shaped double X chromosome. Two kinds of

eggs are accordingly formed (see Text-fig. 21), and when these are fertilized by normal sperms, four combinations result, of which, however, only the yellow XXY daughters and the normal gray XY males are viable.

As first pointed out by Levit and Serebrovsky, later also by Haldane and by Gowen, this peculiar case of maternal inheritance may possibly afford an explanation of a much-discussed exceptional pedigree published by Cuniér in 1839, in which ordinary color blindness, contrary to expectation, is in eleven cases transmitted directly from mother to daughters and to none of the sons. As noted by some of the above-mentioned authors it would be interesting to try to obtain cell division figures from living female members of this Belgian family, by tissue culture, in order to see whether attached X's might possibly be found.

6. THE INTERRELATION BETWEEN GENES AND CHARACTERS. ILLUSTRATIVE CASES FROM MEDICINE

We have so far concentrated our attention on the hereditary mechanism, since an understanding of the basic features in the underlying mechanism is indispensable for any consideration of hereditary disease conditions in man. A last fundamental achievement in this field, the exact mapping of the genes within the



21. Diagram to explain exceptional maternal inheritance. The V-shaped double-X of the female shown in outline. Each of the two attached X-chromosomes carries the recessive gene for yellow body color (y). The paternal X-chromosome in solid black, the Y-chromosome hook-shaped. The cross gives daughters that are yellow like their mother, sons that are gray like their father.

chromosomes, will presently be dealt with (p. 106).

Meanwhile, since the rediscovery of Mendel's work, experimental analysis of a vast number of cases in the most different plant and animal species has provided us with a deeper insight into the relation between genes and characters, which may be summarized thus:

In the simplest cases a particular gene causes a single localized character change. Dominant *ptosis,* drooping eyelids, in man (Plate IV, Fig. 15) or the type of dominant *alopecia,* hairlessness, presented in Plate IV, Fig. 16, may serve as illustrations. Generally, however, this unit character conception on closer examination proves to be a fiction; the hereditary character change on which we primarily concentrate our attention is only one among many less conspicuous alterations caused by the same gene.

This *manifold effect of the genes* is well illustrated by the infantile form of the so-called *infantile amaurotic idiocy,* where the results of a series of different investigators agree in demonstrating that a single recessive gene is responsible for the entire complex of fatal pathological changes, viz., progressive mental impairment, muscular weakness leading to complete paralysis and diminution of visual activity resulting in blindness.

A single dominant gene induces the symptom complex found in the *"blue sclerotics,"* studied, among

others, by Bauer (see Fig. 54, Plate XIV). A thin, transparent and accordingly bluish sclera is here combined with an extraordinary brittleness of bones, dentition anomalies and, in later years, otosclerosis leading to deafness. The heterozygous affected family members are frequent guests in the hospitals. In Oslo a young heterozygous man, turning around suddenly in the street in order to look at the legs of a pretty girl, fractured his leg bone. Another time, when he took his fiancée on his lap, his thigh-bone broke.

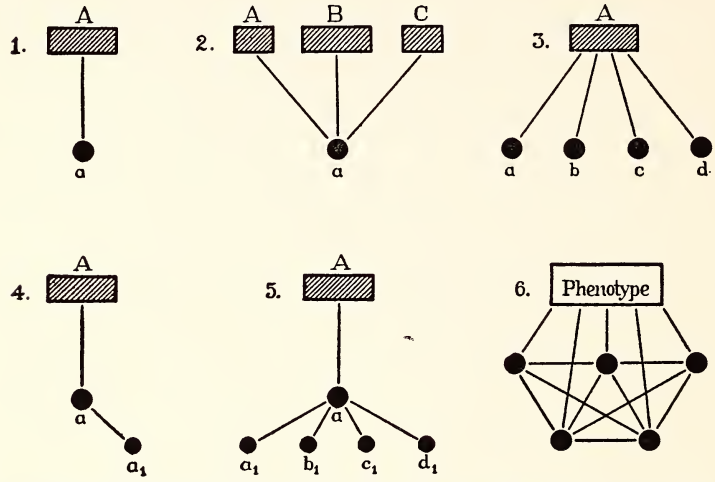
As a last illustration of this type may be mentioned the incompletely dominant *dysostosis cleido-cranialis* in which the striking skull abnormalities presented in Fig. 17, Plate V, are combined with rudimentary collar bones, defective teeth and frequently underdevelopment of the subcutaneous body fat.

In the diagram presented in Text-fig. 22 the above situations are schematized: a single gene, a, causes the character A (1), or more frequently, a single gene, a, induces a series of alterations, A, B, C (2).

More complicated are the cases in which the character change—frequently involving the size or quantity—is not due to *one* gene, but to the coöperation of several genes (3), as disclosed by East and, independently, by Nilsson-Ehle. Such cases are difficult to analyze in man, but a certain indication of their im-

portance may be derived from twin pathology, to be dealt with later (p. 153).

In still other cases the effect of a main gene, a, is enhanced or inhibited by one (4) or more specific



22. Diagram illustrating the interrelation between genes and characters. A-D, characters; a-d, genes. a_1-d_1, modifying genes. For explanation see text. AFTER ZARAPKIN FROM SALLER.

modifying genes (5). The weak type of brachyphalangy mentioned on p. 58 may not improbably be due to the presence of such a specific modifier. The clear-cut Mendelian inheritance of the modifying genes has been established in different experimental material.

In this way there is established what might be termed an internal, genotypical balance or equilibrium, due to the interaction of all the genes of the

individual (6), each gene influencing a certain link in the chain of morphological and physiological processes which insure the normal development and life of the individual in question.

It will be readily understood that a change in a particular gene, by interfering with this normal equilibrium, may very likely induce pathological states of different orders. But before we enter upon a further discussion of this topic (see p. 139) it is necessary to consider how changes in the genes themselves occur.

7. THE ORIGIN OF INJURIOUS GENES BY MUTATION

THE hereditary factors are exceedingly stable, but modern genetics has revealed the fundamental fact that they are not absolutely so. Occasionally it happens that a particular gene undergoes a sudden change, a process known as *mutation;* and if this change takes place in one of the cells of the germ track (see Text-fig. 44, p. 189) then this mutated gene will be transmitted to the offspring, among which individuals may accordingly appear who exhibit the corresponding mutant character. The origin of the white eye color in Drosophila dealt with earlier may serve as an illustration (p. 69).

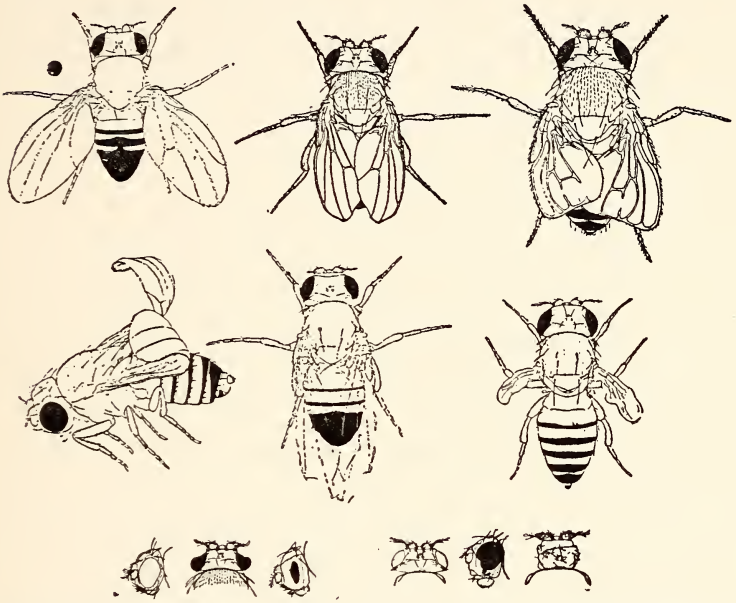
The new hereditary characters arising by mutation may affect any part of the individual. Thus in

Drosophila more than fifty different eye colors are known, of all shades from colorless to deep chocolate; a large series of body colors from the faintest yellow to coal black. The eyes may be enlarged or reduced in size, or entirely lacking. The wings may show the varied alterations of form or venation. The bristles and hairs may be singed or forked, reduced in number or size, or entirely lacking. The legs may show a hereditary tendency to doubling, and the abdomen a series of striking abnormalities. A sample of different mutant types is presented in Text-fig. 23.

Extremely embarrassing to the older comparative anatomists are the mutant races in which the number of tarsi, joints on the legs, are reduced to four instead of the normal five, or races in which the front of the head is provided with a decent pair of legs instead of the normal feelers. In one mutant race the positive phototropism (attraction towards light) is lost, in others the fertility of either males or females.

A large number of mutant genes induce gross abnormalities reducing the viability, and a great many are even lethal when homozygous, or, if sex-linked, lethal for the males in single dose. Particularly interesting from a medical point of view are some mutant genes which cause the formation of malignant, pigmented tumors which kill the larvæ (see Text-fig. 32, p. 142).

That so many mutant genes are injurious and even fatal in their effect is very natural. A sudden change in the delicately adjusted genotypical balance is more likely to upset than to strengthen the mechanisms on

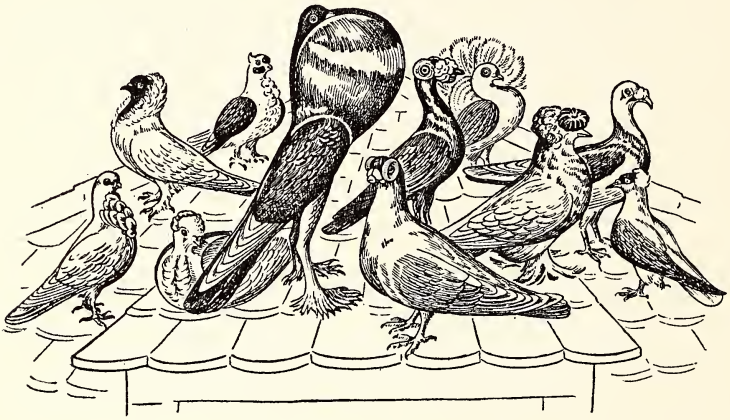


23. Sample of hereditary wing and eye characters that have arisen by mutation in Drosophila. FROM MORGAN.

which the normal functioning of the organism depends.

Each of these hereditary deviations is due to a localized change in one of the chromosomes affecting one gene only, a so-called *point mutation*. Though rare, such mutations occur in any plant or animal material,

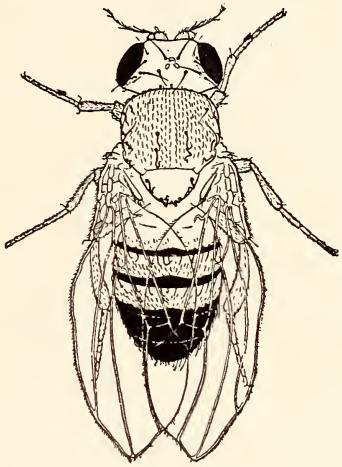
in nature as well as under domestication. In the domesticated forms such mutations have been preserved by selection and constitute a main basis for the rich variety of our utility or fancy breeds, as for instance in dogs or in pigeons (see Text-fig. 24). We are fully justified in concluding that the hereditary characters in man also owe their origin to the same process.



24. Sample of different fancy breeds in pigeons produced by selection and combination of mutant characters. AFTER PRÜTZ FROM WEISMANN.

While the ordinary mutations, the "point mutations," involve a change in a particular gene, genotypical changes may also involve a section of a chromosome (cf. p. 113) or entire chromosomes. Such changes are denoted as *"section mutations"* and *"chromosome mutations."*

Mutations, however, do not only occur in the germ cells. They may also occur in ordinary body cells at different stages of development. If the new mutant gene is dominant, then the corresponding character change will appear only in that part of the organism which by ordinary cell divisions is derived from the



25. Male Drosophila mosaic due to a recessive and sex-linked somatic mutation inducing "singed" bristles. Dorsal surface of thorax, left legs and left half of abdomen singed bristles. Head, right legs, right half of abdomen normal straight bristles. The fly is homozygous for an autosomal mutant gene that makes the wing blades curved. FROM MOHR.

mutated cell, leading to the production of a limited mosaic area of greater or smaller size, depending upon whether the mutation occurred early or late in the development of the individual. If the mutant gene is a sex-linked recessive an analogous mosaic area will ap-

pear in males only (see Text-fig. 25). In their effects these point mutations in the body cells may be difficult to distinguish from section or chromosome mutations which may also occur in somatic cells and lead to the appearance of mosaic areas.

These so-called *somatic mutations* have provided us with a simple explanation of some puzzling cases of *mosaicism in man,* as for instance a brownish sector in an otherwise bluish iris, a grayish spot in otherwise dark hair, etc., anomalies which were formerly entirely unexplainable. For further illustrations the reader may refer to p. 94 and p. 201, and to Fig. 14, Plate IV and Figs. 61 and 62, Plate XVI. That somatic mutations are of interest in connection with the tumor problem we shall see later.

Meanwhile we have to consider briefly a last fundamental point in the chromosome mechanism in order to get a somewhat deeper insight into the finer architecture of the germinal material.

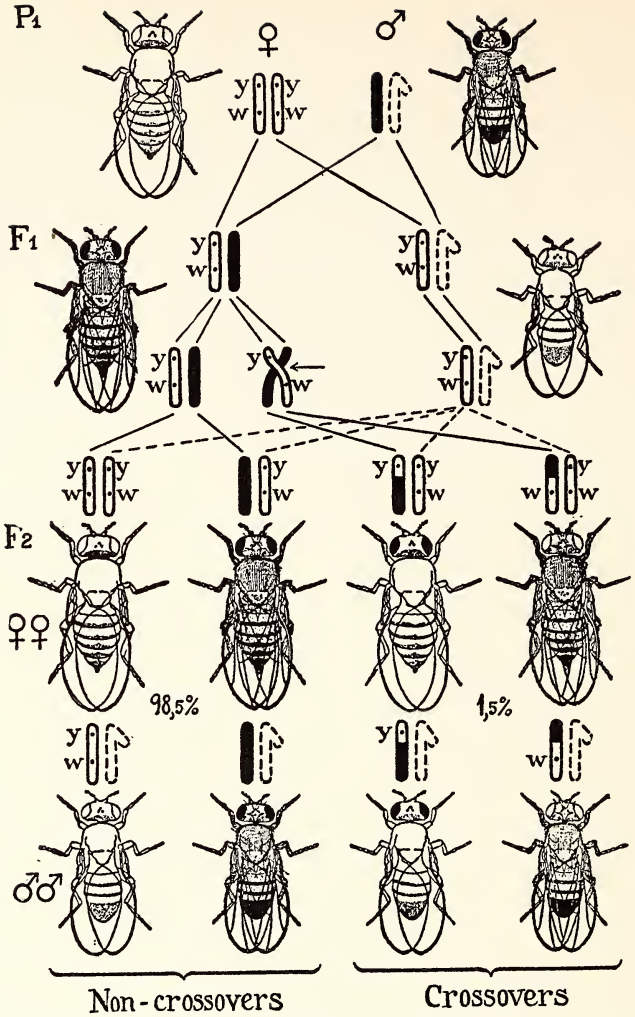
8. LINKAGE AND CROSSING OVER. CHROMOSOME MAPS

We remember how genes belonging to the same linkage group, i.e., genes which are located in one and the same chromosome, have a tendency to stick together in inheritance (cf. p. 85). This tendency is definite and regular but not absolute.

If a female homozygous for the sex-linked recessive mutant genes for yellow body color and white eyes is mated to a normal, i.e., gray, red-eyed male, all the sons will be yellow and white-eyed, since they receive an X-chromosome with both these genes from their mother. The Y-chromosome which they in addition receive from their father does not prevent their manifestation. The daughters, however, are gray and red-eyed since in addition to the maternal yellow white X they receive a normal X with the dominant allelomorphs, determining gray body color and red eyes, from their father (Text-fig. 26).

When such a heterozygous F_1 female is crossed to one of her yellow white brothers, we might expect that half her sons would be yellow white, since they receive an X with both these genes from their mother. Likewise, we might expect that half of the daughters would be yellow white, since they receive two X-chromosomes with both these genes, and accordingly carry them in double dose (see Text-fig. 26).

However, if we carry out the actual experiment, the result is somewhat different. It is true that the large majority among their sons and daughters, in fact 98.5%, are found to be either yellow white or gray red, as the grandparents. But in addition we obtain some sons and some daughters that are yellow red-eyed



26. Crossing over. Back-cross of heterozygous F_1 female (out of P_1 yellow, white-eyed female × gray, red-eyed male) to yellow, white-eyed male. The maternal X-chromosome with the recessive genes for yellow body color (y) and white eyes (w) shown in outline; the paternal X with the dominant allelomorphs (non-yellow, non-white), in solid black. The hook-shaped Y-chromosome in dotted outline. Below, the resulting non-crossover and crossover classes. An arrow indicates the point where a break followed by exchange of chromosome sections takes place. AFTER MORGAN.

or gray white-eyed!—both classes in equal numbers. Based on such experiments comprising more than 200,000 flies, these exceptions, denoted as *crossover individuals,* comprise with remarkable regularity 1.5% of the total output. The 98.5% among the offspring which show the same character combinations as the grandparents are *"non-crossover individuals."*

This experiment demonstrates that yellow and white do *not* show free Mendelian segregation as did the characters rough and colored in the cross of guinea-pigs (p. 79). They have in a large majority of cases kept together in inheritance, they are linked. But in 1.5% of the cases the linkage is broken, so that the two genes which entered the experiment together have been separated.

If instead of yellow we use another mutant character, crossveinless wings, in an analogous experiment, it is found that white and crossveinless separate, not in 1.5%, but in 12% of the cases. White and crossveinless are in other words more loosely linked than are yellow and white.

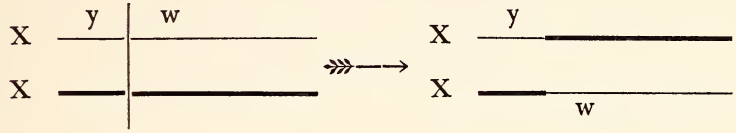
Further, if we know these values for yellow and white and for white and crossveinless respectively, then we are able to *predict* that an analogous experiment involving yellow and crossveinless will give 1.5% plus or minus 12% of crossover individuals. If the ac-

tual test is carried out we obtain as a matter of fact with great regularity 13.5% of crossovers. And just as we are able to break the linkage between two genes belonging to the same linkage group, we may bring together in one individual, in a corresponding percentage of cases, such genes when they enter the cross from indifferent grandparents. If for instance we mate a yellow female by a white-eyed male and raise an F_2 generation, 1.5% of her grandchildren will be *both* yellow *and* white-eyed.

The explanation of these phenomena, which were first detected by Bateson and Punnett, we owe to Morgan and his co-workers (among whom Sturtevant should be particularly mentioned in this connection). *The genes are arranged in linear order along the chromosomes,* like beads on a string. Previous to the reduction division the two members of each chromosome pair are, as we remember, temporarily associated lengthwise. During this stage transverse breaks occur along the chromosomes, followed by mutual exchange of the resulting fragments, the process denoted as *crossing over.*

If such a break, followed by interchange, occurs within the distance between two mutant genes present in one and the same member of the two associated chromosomes, as for instance between yellow and

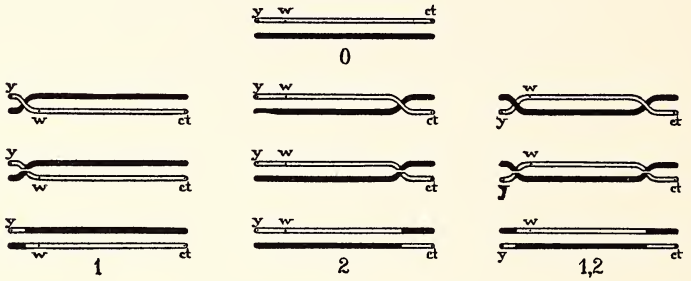
white in the F_1 female, Text-fig. 26, then these two genes will separate. One of the resulting X-chromosomes will contain the yellow, but not the white gene, the other will contain the white, but not the yellow gene, thus:



Other things being equal, such breaks will clearly occur more frequently between genes which are in distant parts than between genes which lie close together. In our examples such a crossing over has occurred in 1.5% of the cases in the yellow-white test, in 12% of the cases in the white-crossveinless test. That an analogous yellow-crossveinless test gives 13.5% of crossovers is in accordance with expectation, since, if the genes are in linear order, the distance between the genes A and C can only be either, as here, the sum of, or else the difference between their distance from a third gene B.

The percentage of crossing over is in other words an expression of distance, and we are able to measure the chromosomes genetically, the distance corresponding to 1% of crossing over representing the unit in this genetical system of measurements.

By aid of crossing over we may bring numerous genes belonging to the same linkage group together in one chromosome, and by aid of such "marked" chromosomes it is possible to demonstrate that *it is always large blocks of genes, that is, entire chromosome sections that are exchanged.* If in such crossing over ex-



27. Diagram to show the X-chromosomes produced by a Drosophila female that in one X-chromosome carries the genes for yellow body color (y), white eyes (w) and cut wings (ct). At the top, the non-crossover chromosomes (O). Below, the chromosomes resulting from crossing over within the y-w section (1), within the w-ct section (2), and double crossing over, i.e., crossing over within the y-w and the w-ct section simultaneously (1, 2).

periments we use chromosomes that are "marked" by genes that occupy loci that are sufficiently apart, it is also found that crossing over may occur at more than one point of a chromosome simultaneously, "double crossing over." The chromosomes resulting in such a "three point experiment" are presented in Text-fig. 27.

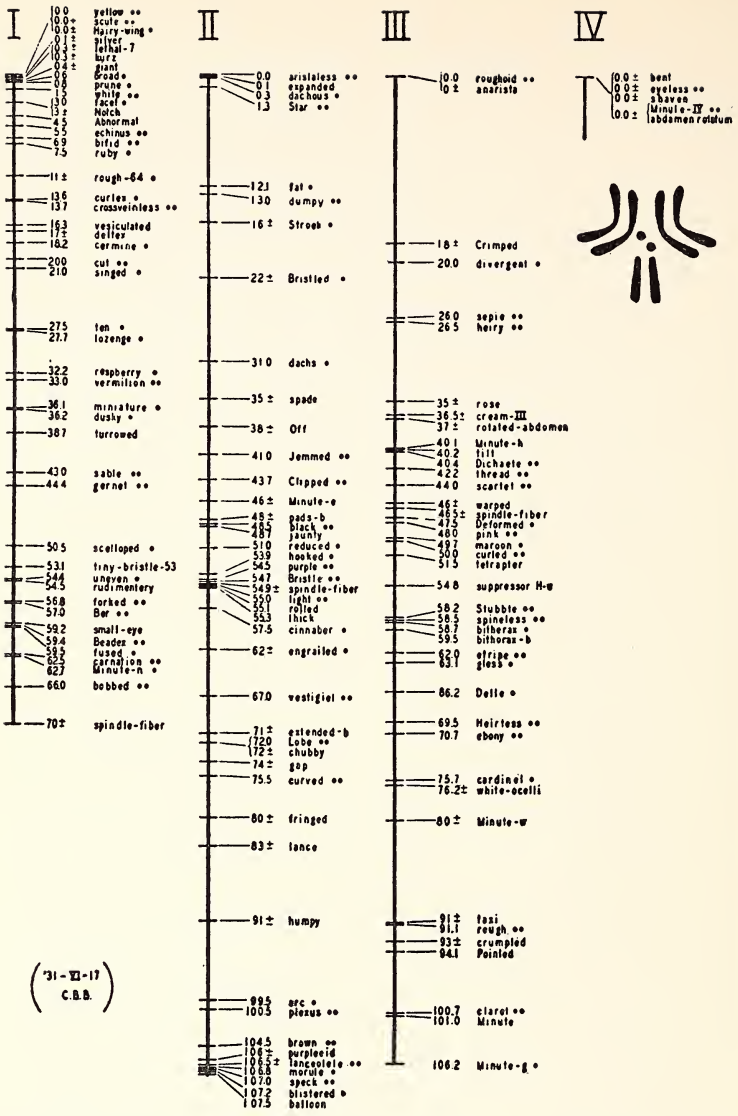
What has been said applies not only to the sex chro-

mosomes, but to the autosomes as well. A great advantage is involved in the fact that crossing over in Drosophila only occurs in females, never in the males. This makes the results much easier to analyze.

By aid of the crossing over percentages derived from a steadily increasing amount of experimental data it has thus been possible to build up detailed *maps for each chromosome,* in which the relative location of the genes of each linkage group is plotted. (See Text-fig. 28.) These chromosome maps represent the basis of all genetical work in Drosophila. Not only are several of the results presented due to the use of these maps, but they have also rendered possible the most detailed analysis of a series of cases in which a particular section of a chromosome has been lost or is present in duplicate, has been inverted, or translocated from one chromosome to another, "section mutations," the combined genetic and microscopic analysis of which has definitely proved the reality of the chromosome maps.

That physical crossing over actually takes place has finally been proved by Stern in Drosophila and by Creighton and McClintock in maize by aid of the same combined method, in experiments involving two chromosome partners which owing to such section aberrations were visibly different.

When we remember that the Drosophila chromo-



28. Chromosome map of the location of the genes in the Drosophila chromosomes. To the right, female equatorial plate showing the actual size of the chromosomes. I, the rod-shaped X-chromosome; II and III, the long, V-shaped autosome; IV, the small round autosome. AFTER BRIDGES FROM MORGAN.

somes are so small that they must be enlarged about 2,000 times in order to be seen distinctly, it may probably be conceded that this detailed mapping of the chromosomes represents a real triumph of the human mind. At present the geneticists are engaged in an analogous mapping of the chromosomes in a series of other organisms, including mammals. Thus, at the last International Genetics Congress at Ithaca, the "field map" of the maize chromosomes, presented in Plate V, Fig. 18, with living mutant representatives of each particular locus, was rightfully considered one of the great events.

In connection with this presentation of some of the main facts on which the mapping of the chromosomes is based, it should be emphasized that the unit in the genetic length measure is not a metric unit. Different evidence indicates that the frequency of crossing over is not identical in all parts of a chromosome, and other factors, such as age (Bridges) or temperature (Plough) may also influence to some extent the crossing over frequency.

By combined genetic and microscopic analysis of visible translocated chromosome sections produced by X-rays (see p. 192) Muller and Painter, as well as Dobzhansky, have now been able to construct actual metrical chromosome maps, which also take the dif-

ferences in crossing over frequency in different regions of the chromosome into account. And recently Heitz and Painter, quite independently, have even succeeded in detecting distinct differences in the staining reactions of the "segments" of which each chromosome is built up, visible differences in relation to which Painter has been able to plot the actual location of the mutant genes.

These last astounding advances in the field of chromosome mapping coincide in demonstrating that, though the frequency of crossing over is not the same near the ends as in the middle of the chromosome, the relative, mutual location of the individual genes is without exception identical with the one previously determined by crossing over experiments. *The linear order of the genes and the validity of the chromosome maps are in other words no longer hypothetical conceptions, but actual, indisputable facts.*

9. UNI-LOCAL GENES. THE HUMAN BLOOD GROUPS

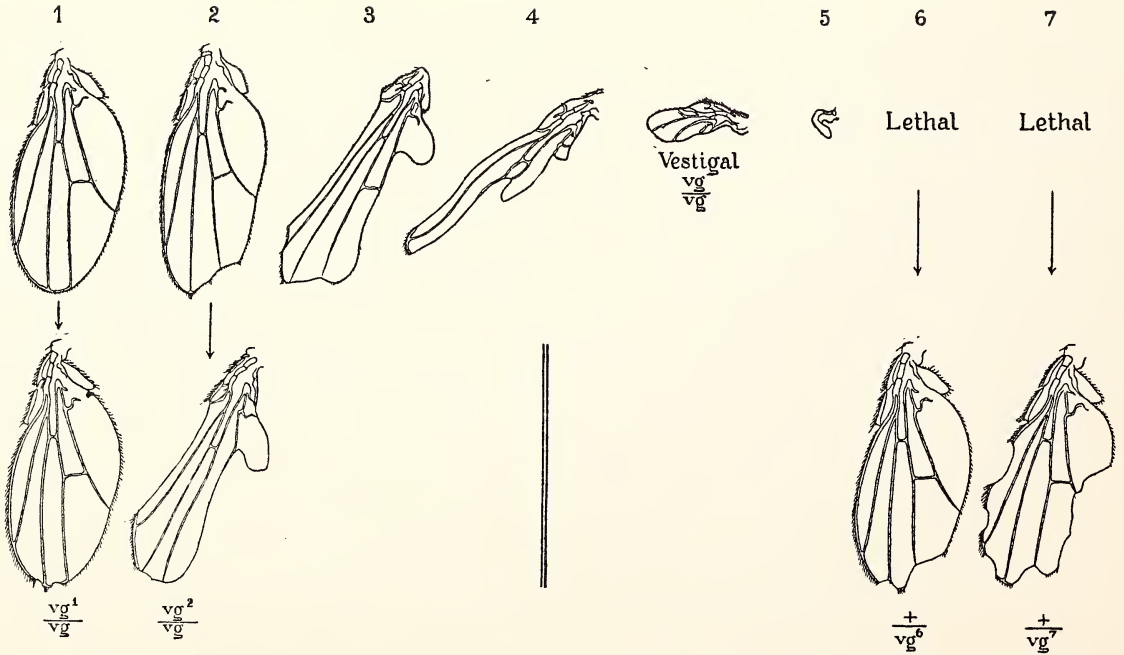
THE mapping of the individual genes has revealed the fact that the locus of a mutant gene bears no relation to the part of the individual which is affected. Genes which are located close together may affect very different parts, or may affect the same part very differently. Conversely, genes located in different chro-

mosomes may have indistinguishable somatic effects. One and the same pathological trait or even symptom complex may well be induced by different genes.

Each normal character, on the other hand, depends for its development upon the normal coöperation of many different genes. The red eye color in Drosophila, for instance, depends on many genes located in different chromosomes. Each of these acts as a differential in the processes that produce the eye color. If one of these genes changes by mutation, the eye color will be abnormal.

Further, some genes are much more apt to undergo mutation than others. But a mutation in one particular locus does not always lead to the same *degree* of character change. In this way *series of uni-local genes,* so-called *multiple allelomorphs* arise, comprising different genes which influence the same character or character complex to a different degree.

Since they are uni-local, *not more than two members of such a series, one in each of the two chromosome partners, may be present in one individual at a time.* When two different uni-local genes are present in one individual they have in most cases a compound effect, i.e., the character change produced is intermediate between those induced by each of the genes when homozygous. The series of multiple allelo-



29. The effect on the form of the wing blade produced by eight different allelomorphs in the vestigial locus. Above, the homozygous types. Below to the left, compounds with vestigial (vg) of two of the weakest recessive allelomorphs (vg^1 and vg^2). Below to the right, the effect of two of the dominant allelomorphs in heterozygous condition. The allelomorph for normal wing indicated by +. In the symbols the spaces above and below the line indicate the two members of the chromosome pair. FROM MOHR.

morphs at the so-called vestigial locus in Drosophila (Text-fig. 29), which affect the wing in different degrees, may serve as an illustration. To the left of the homozygous vestigial type are weaker recessive allelomorphs, one of which has no visible effect unless in combination with the more potent vestigial gene (to the left below). To the right in the diagram are dominant members which are so potent that they produce slight incisions when heterozygous (below), and kill the individual in homozygous condition (above).

Multiple allelomorphism no doubt represents one of the explanations of the frequent occurrence of different familial types of one and the same hereditary abnormality in man. As shown by Bernstein this phenomenon also provides us with a consistent explanation of the inheritance relations of Landsteiner's classical normal *blood groups* which have an ever-increasing practical importance in legal medicine (paternity cases).

Agglutination (clumping of the red blood corpuscles) which occurs when bloods from certain individuals are mixed is caused by the meeting of a specific substance, the *"receptor," in the blood cells* of the one individual with another substance, the *"agglutinin"* present *in the serum* of the other individual. With respect to their equipment with these substances

all individuals belong to one of the following four *"blood groups":*

A-individuals (receptor A; agglutinin anti-B)
B-individuals (receptor B; agglutinin anti-A)
AB-individuals (receptor A and B; no agglutinin)
O-individuals (no receptor; agglutinins anti-A and anti-B)

Whenever a receptor meets the corresponding agglutinin (e.g., when A meets anti-A) clumping results. A and anti-A, B and anti-B may accordingly not coexist in the same individual. By testing the blood of one individual with blood cells and serum from individuals of known blood-type, the blood group to which the individual belongs may be determined.

These four blood groups are inherited as Mendelian differences dependent upon three uni-local genes, A, B and R, of which the two former are dominant, the latter recessive. A-individuals may accordingly be either homozygous or heterozygous for the A gene, B-individuals correspondingly either homozygous or heterozygous for the B gene; AB-individuals have both the gene A and the gene B, while O-individuals are homozygous for the recessive gene R. As shown by Thomsen the A-type includes two sub-types dependent

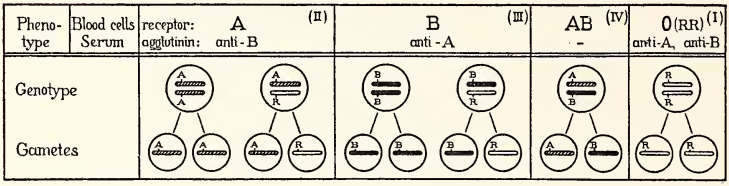
on two different A-allelomorphs, the stronger A^1 and the weaker A^2, but these sub-types are here disregarded.

In the diagram Text-fig. 30 the four classical blood groups (phenotypes) and the corresponding six genotypes are indicated. The salient point is that not more than two of the uni-local genes A, B and R may be present in one individual at a time .The diagram needs no further comment when we remember that the dominant genes A and B show the remarkable relation that both of them, when combined in the AB-individuals, manifest their full effect.

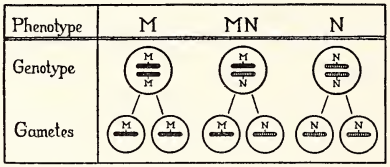
When we consider the germ cells produced in each combination (cf. Text-fig. 30) it is clear that if, for instance, a mother is RR and her child belongs to the blood group A, then this child must have received the A gene from the father, who accordingly cannot belong to the O or the B group, and so on. Hence, by determining the blood group of mother, child and alleged father, falsely alleged paternity may in some cases be exposed.

Landsteiner and Levine have also detected three additional blood types, M, MN and N, which are diagnosed by the (rabbit) immune sera anti-M and anti-N, and which depend upon two dominant genes, M and N. These genes represent an ordinary pair of Men-

The classical blood groups.



The M-N system



A dominant
B dominant
R recessive

M dominant
N dominant

30. Diagram to illustrate the genotypes of, and the germ cells produced by individuals belonging to each of the four different blood groups. The chromosomes carrying the three uni-local genes A, B and R differently marked. Below, the M-N system with the M N factor pair located in another autosome pair.

delian allelomorphs, each of which manifests its effect when combined in MN individuals, (cf. Text-fig. 30.) If a mother is NN and her child MN then the child must have received the M gene from the father who accordingly cannot belong to the NN type, and so on. As shown by Bernstein and by Wiener the M and N allelomorphs are located in another chromosome pair and therefore show free Mendelian segregation with the classical blood group genes. Analogous genes in the rabbit, discovered by Levine and Landsteiner, have been studied by Castle and Keeler.

By combination of the two tests it is now, according to Waaler, possible to clear up about one-third of the cases of falsely alleged paternity. It should be emphasized that by these methods *we are never able to pick out a particular man as the father of the child in question.* But in one-third of the cases we may *exclude* a particular man being the father of this child. In two-thirds of the cases the blood group tests will give no answer in either direction.

A number of authors have tried to find out whether other physiological or pathological conditions show any connection with particular blood groups. One author even believed he had found typical differences in the duration of defecation among persons belong-

ing to different blood groups: "bei A nur bis wenige Minuten, bei B oft lange Zeit, 20—40 Minuten, in der Mitte steht die Gruppe O"! But since a recent critical review of this literature by Thomsen, from which the last quotation is derived, leads to entirely negative results with regard to the connection of the blood groups with pathological states, a further consideration of the blood groups falls outside the scope of the present book.

It is, however, of interest to know that the common occurrence of two sets of independent autosomal serological characters opens up certain possibilities for a mapping of the chromosomes by application of the blood tests to all individuals in families where good autosomal hereditary traits occur. Since we have in man 23 pairs of autosomes, the chances of any other autosomal gene being located in either the A-B or the M-N chromosome pair is as 2 : 23, or 1 : 11.5.

That linkage occurs in man may not only be concluded from its general occurrence in other forms, but is also evidenced by the numerous traits which show sex-linked inheritance. Davenport calls attention to a case described by Madlener, in which hæmophilia and color blindness were both present in the affected males and transmitted as linked characters through four gen-

erations. Since color blindness is fairly common, a search for color blind individuals ought to be carried out in families where other sex-linked traits are being investigated.

CHAPTER IV
SPECIAL TOPICS

1. REPRESENTATIVE CASES OF HEREDITARY DISEASE CONDITIONS IN MAN

WITH this general knowledge of the genes and their distribution in mind we may now consider some typical cases among the rapidly increasing number of recorded hereditary pathological states in man.

A varied body of material may be derived from *ophthalmology,* the field of eye diseases. In the development of the eye the formation of a double walled "optic cup" from the brain (giving rise to the retina) is correlated with the development of a lens from quite another source, viz., the superficial layer of the skin. It is easily understood that a gene which affects the rate of development of either of these components may very likely interfere with the delicate normal adjustment and lead to eye abnormalities of very different type and degree.

The technique of diagnosis in ophthalmology is also particularly refined, so that even slight alterations are likely to be recognized and properly described. Waardenburg's recent splendid monograph on hereditary eye characters only, constitutes a big volume, larger than most ordinary text-books.

Of *microphthalmus,* underdevelopment of the eyeball, which in some cases leads to blindness, a considerable number of both dominant and recessive types has been recorded. One case studied by Ash showed typical sex-linked inheritance. As might be expected, the microphthalmic condition is frequently combined with *coloboma,* "cleft iris"; in some cases also with *cataract,* opaque lens, or *lens luxation.*

During the earlier developmental stages the optic cup has normally a defect downwards so that the rim of the cup is incomplete in this region. Later this defect, the chorioidal fissure, closes up so that a real cup is formed. The rim of this cup corresponds to the pupillary margin in the fully developed eye. Disturbances of the closure of the chorioidal fissure will lead to defects in the lower part of the iris, denoted as *coloboma* or "cleft iris" (see Plate V, Fig. 19). Numerous hereditary cases of varying degree and symmetry have been described, among others a dominant case covering five generations (Snell).

In one case coloboma was combined with almost complete *aniridia,* lack of iris, a malformation which also in its pure form exhibits clear-cut dominant inheritance in man (W. Clausen, Lawrentieff). The reverse condition, a dominant extreme *miosis,* narrow pupilla, due to failure of development of the dilatator muscle, has been described in Norway by Berner and Holth.

Of hereditary *degeneration of the macula,* the most light-sensitive spot of our retina, both dominant cases and recessive sex-linked cases of different types and different ages at onset occur, and the same is true of *retinitis pigmentosa.* Of this progressive degeneration with pigment deposits along the peripheral retinal vessels, Bell has collected no less than 366 pedigrees from the literature. Some of the autosomal recessive types are in 22% of the cases associated with deafness (de Wilde), a fact which demonstrates the manifold effect of the gene involved.

The sex-linked recessive *optic atrophy,* which especially affects the papillomacular fibers of the optic nerve, is very fatal in its consequences. This condition is called *Leber's disease.* Certain observations by Waardenburg indicate that this lesion, which generally develops after puberty, may also occasionally affect heterozygous women.

Congenital *night blindness,* "moon eye," is one of the clearest examples of simple dominant inheritance; Nettleship's famous pedigree of the French Nougaret family now having been extended to cover no less than ten generations. Recessive sex-linked cases are, however, also known.

The best example of sex-linked inheritance in man is provided by ordinary *red-green blindness,* of which a steadily increasing number of pedigrees has been recorded since Horner's classical observation. When critically revised, as has been done by Schiötz, the evidence is found to conform to the expectation perfectly (see further on this point p. 72).

By aid of the so-called anomaloscope four distinct types of red-green blindness may be distinguished: deuteranomaly or "red-sightedness," deuteranopy or "green blindness," protanomaly or "greensightedness" and protanopy or "red blindness." As shown by Waaler, the two former in combination with the normal allelomorph for normal color vision form a series of multiple allelomorphs (cf. p. 117), deuteranomaly dominating over deuteranopy, and the normal allelomorph over both of the others. The corresponding is true of protanomaly and protanopy, which are members of another allelomorphic series, in which pro-

tanomaly dominates over protanopy, and the normal allelomorph over both the others.

Cases have been encountered by Döderlein, Hess, Göthlin and Waaler in which a woman with normal color vision produced both protanopous and deuteranomalous sons, a fact that demonstrates that the two series of allelomorphic genes are in different loci in the X-chromosome. If not, such a woman would be color-blind herself.

Of more serious lesions, eventually leading to blindness, may be mentioned dominant cases and recessive sex-linked cases of *glaucoma,* abnormally high internal tension in the eye ball which if not operated upon leads to blindness; recessive cases of *hydrophthalmus,* "bull eyes"; and a large number of hereditary cases of *cataract,* mostly dominant but of very different types and time of onset. No doubt a very considerable number of the inmates of our blind schools are genetically blind.

In addition to these cases, most of which may be explained as due to disturbances of the normal growth or differentiation of particular embryonic components of the eye, numerous cases are also encountered in which the eye alteration is only a partial expression of more generalized anomalies.

We have formerly (p. 63) mentioned *albinism,* which involves the entire outer germ layer, the ectoderm. A well-known example of a dominant genetic abnormality which seems to affect the mesenchyme, part of the middle germ layer, in an elective way, is represented by the "blue sclerotics," also previously considered (p. 98). A very remarkable abnormality has been studied by Marfan, Weve and others, in which a strange type of hand form, denoted as *arachnodactyly* or "spider fingers" is combined with lens luxation. (Plate V, Fig. 20 and Plate VI, Fig 21.) As an example of simultaneous affection of eye and central nervous system, the recessive *infantile amaurotic idiocy,* leading to muscular paralysis, blindness and idiocy, (cf. p. 98) may be quoted.

In the field of *neuropathology* (nerve diseases) different hereditary types of *progressive* muscular, neural or spinal *dystrophies,* of *spastic spinal paralysis* and *paraplegia,* of *spinal ataxia* (Friedreich's type) and *cerebellar ataxia* occur, conditions which all involve paralysis or lack of coördination of different parts of the muscular system. Further, *Huntingdon's chorea,* "St. Vitus' dance," associated with progressive mental disturbances is typically dominant, while the progressive *hepato-lenticular degeneration,* known as *Wilson's*

disease (Plate VI, Fig. 22), in which both the liver and one of the so-called basal ganglia of gray matter in the brain are simultaneously affected, is recessive.

In this field of medicine deviations from orthodox Mendelian inheritance are frequently encountered among the dominant cases and in these the degree of manifestation and the time of onset vary widely both with age and undoubtedly also with environmental influences. A man who carries such a gene in heterozygous condition may, for instance, die before he himself has reached the critical age. He will accordingly be put down in the records as normal. But before his death he may have transmitted the gene to some of his children, who accordingly develop the pathological condition in later life. Differences in the hormonal or external environment may account for differences in frequency or degree of one and the same anomaly in the two sexes.

The large body of evidence on hereditary *deafness* indicates clearly that congenital deafness may be induced by different simple recessive genes, and also deafness in later life due to *otosclerosis* seems in quite a few cases to be most easily explained on the basis of a single recessive gene. A complication in these investigations is involved in the fact that deafness in quite a few cases is adventitious, an acquired character re-

sulting from diseases that have affected the individual even during infancy.

As a simple illustration of variation in the degree of manifestation of one and the same dominant gene in man may be cited the cases in which *harelip* on one or on both sides, or cleft palate, or both together occur in different members of the same family, (Plate VI, Fig. 23). The abnormality is due to a hereditary failure of fusion of the facial processes which during embryonic life form the nose, the upper lip and the roof of the mouth, a situation that is paralleled by Reed's evidence from an analogous mutation in the house mouse.

As regards *metabolic derangements* in man, Pincus and White, after a statistical treatment of Joslin's large material, arrive at the conclusion that *diabetes mellitus* is inherited as a recessive. But incomplete dominant cases are also known, and it would be interesting to investigate the blood sugar content in the normal members of such families in order to see whether some of them might not possibly have a slight increase of the blood sugar, which eventually, under unfavorable environmental conditions, might be replaced by real, manifest diabetes. According to Macklin, in investigating the blood sugar of 40 supposedly normal relatives

of 23 of his diabetic patients Sherill discovered diabetes in 21 of the number (see also p. 160).

Dominant cases of the benign *orthoglycæmic glycosuria,* "leaky kidneys," have been recorded. A clear-cut dominant is *diabetes insipidus,* characterized by an enormous increase in the daily amount of urine produced, presumably due to a hereditary dysfunction of the middle part of the pituitary body, a gland attached to the base of the brain. A clear-cut recessive is the rare condition known as *alkaptonuria.* The presence of a particular acid causes the urine of such patients to darken on exposure to air.

The hereditary cases of *hæmatoporphyrinuria, cystinuria* and *hæmorrhagic nephritis* are less clear, while hereditary *hæmolytic jaundice* with spleen enlargement shows incomplete dominant inheritance, as does also an autosomal hæmophilia-like condition described from Russia by Levit and Serebrovsky.

A typically dominant anomaly is Quincke's *angioneurotic œdema,* the outstanding symptom of which is a sudden swelling of skin or mucous membranes. If this swelling affects vital organs (e.g., the larynx) the individual frequently dies from the disease. In a family studied by Crowder and Crowder where angioneurotic œdema showed clear-cut dominant inheritance through five generations the condition ended

fatally in no less than 15 out of 28 affected family members.

In cases of this sort, denoted as cases of *allergic hypersensitiveness,* attacks are frequently brought on by exposure to particular environmental stimuli. Thus some individuals develop hay fever when exposed to pollen from particular plants; in others the emanations from certain animals, as for instance horses or cats, induce asthma; in still others particular substances in the food, in strawberries, lobsters or a variety of other foods, call forth skin eruptions, gastro-enteritis, asthmatic symptoms, etc.

The mechanism back of these remarkable phenomena may be briefly presented thus: the critical substance in the food, in emanations, etc., is called the *allergene.* When certain individuals are exposed to this allergene, a specific so-called *antibody* is formed in their body cells. The presence of this antibody makes the tissues of the individual *hypersensitive, allergic,* towards the corresponding allergene, when this is introduced through the food or eventually through the air.

This represents a complication in dealing with the hereditary relations of such cases. From case histories it seemed obvious that different types of protein hypersensitiveness in man were inherited. But recently

Ratner showed that both native allergenes and sensitizing antibodies may in pregnant women pass through the placenta and enter the blood of the fœtus. A hypersensitiveness in the child, which gives the impression of being inherited, may in other words also simply be an acquired character due to the environmental contact in utero. The case represents a good illustration of the sources of error encountered when it is a question of deciding whether a particular state is genotypical or simply due to the environment.

As regards the question of *hereditary immunity,* or resistance to particular diseases, a varied body of evidence both from plants and animals indicates that such an immunity may be distinctly hereditary. The following case may be quoted as an interesting illustration: The wild swine is immune towards "Schweineseuche," a bacterial lung disease caused by *bacillus suisepticus,* which is extremely devastating in ordinary domesticated pigs. By crossing different German and English domesticated breeds to Russian wild swine, Ossent has recently succeeded in demonstrating that among the descendants in later generations those individuals which inherited the wild-type coat color are immune to the disease, in contrast to the others which all perished. The experiment was carried out in an old barn

which had for a long time been thoroughly infected with the specific bacillus.

In man, the West African negroes are relatively immune to yellow fever, while conversely the red Indians seem to have a lowered resistance to ordinary measles which accordingly for them represents a rather severe disease. Clinical experience on individual resistance to measles, diphtheria, whooping-cough, etc., fall well into line with experimental evidence on hereditary immunity as derived from the study of rust-resistant strains of wheat, or strains of poultry or mice which are immune to fowl typhoid or mice typhoid respectively. But owing to the all-prevailing crossbreeding in man it would be very difficult to obtain a conclusive demonstration of inherited immunity in this material. How investigations on twins may here give certain hints will be explained later.

These examples of monofactorial Mendelian inheritance of pathological states might easily be supplemented by an ever-increasing number of cases from different fields of pathology, *dermatology* (skin diseases),—a large and very complete treatise on inherited abnormalities of the skin has recently been published by Cockayne—, *otology* (ear diseases), *orthopedics* and *dentistry;* but the above may suffice for our present

purpose, which is to give an idea of the manifold ways in which genes may interfere with the normal morphological or physiological processes. Some outstanding cases from the last-mentioned branches of medicine will be considered in other connections.

Meanwhile it is of interest to note that a large number of mutations which parallel those encountered in human material are now known in laboratory mammals, where their mode of action may be thoroughly analyzed. As a matter of fact, thanks to the inexhaustible peculiarities of the human mind, particularly repulsive pathological traits have not infrequently been selected as standard characters for entire breeds in our domesticated animals, as for instance in dogs. Think for instance of the nasty little Pekingese or the bulldog! The outstanding bulldog champions at the exhibitions have been delivered by the aid of forceps or by Cesarean section, since the enormous, thoroughly deformed head and the narrow pelvis demanded by the standard seriously interfere with, or absolutely prevent normal delivery. Other examples of selection of pathological traits as standard factors will be met with when we consider another question of increasing importance for genetics and pathology, namely, the question of lethal genes.

2. LETHAL GENES. THEIR OCCURRENCE IN MAN

Generally speaking, the mutations in any material are distributed over a spectrum, according to the degree of the visible changes produced—to use an image introduced by Muller.

At the left extremity of this spectrum are found those mutations which fail to produce any visible character changes, but which cause physiological alterations or act as modifiers of other genes.

Through a series of gradual steps these subliminal mutations are connected with those mutations that produce sufficiently pronounced character changes so as to manifest themselves externally. These mutations are the ones which we use as our implements in genetical experiments. This central part of the spectrum is comparatively narrow. In the majority of these mutants the pheno-typical alterations are already extensive enough to lower the viability of the individual in question.

Again through a series of very gradual steps this middle part of the spectrum is connected with the right extremity. The mutants found here produce such extreme alterations that they have a fatal or almost fatal effect. As a general rule there is a very high correlation between pronounced character changes on one

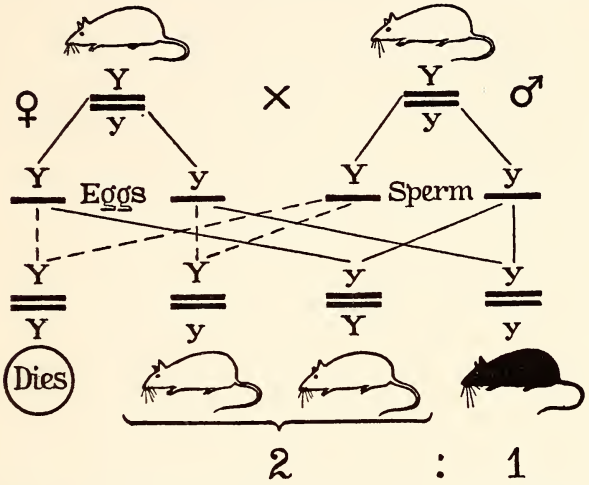
side, and lowered viability on the other. And the number of harmful, and especially of lethal mutations is many times the number of beneficent mutations.

This relatively frequent occurrence of lethal mutations is to be expected since living organisms are highly complicated machines, the effective functioning of which depends upon the undisturbed interlocking of many wheels. Therefore, a sudden change arising through mutation may very probably interfere with the normal functioning and eventually stop the entire machine.

We distinguish between two kinds of lethal genes: *recessive lethal genes* and *dominant genes with lethal effect*. The former have no detectable influence in single dose, but kill the individual when homozygous. The latter produce slight character changes when heterozygous, and kill the individual in double dose.

The first lethal gene, discovered by Cuénot in 1905, belonged to the last category. He found that it was impossible to raise mice that were homozygous for the dominant yellow body color. Yellow mice are always heterozygous. When inbred they give yellow and non-yellow individuals in a 2 : 1 instead of the normal 3 : 1 ratio, since all the homozygous yellow individuals die as embryos (see Text-fig. 31). These degenerating yellow homozygotes have later been found in the uterus.

This case makes us at once acquainted with the outstanding criterion of the presence of a lethal factor, namely, the elimination of particular expected classes. We owe to Morgan and his associates a further analysis of the lethal genes. In Drosophila the first lethal genes

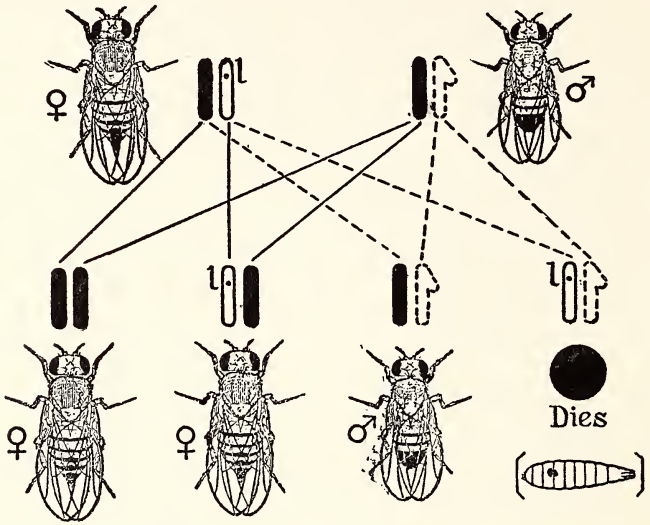


31. Diagram to illustrate the lethal effect of the dominant gene (Y) for yellow coat color in mice. y, the recessive allelomorph. Yellow mice shown in outline, non-yellow mice in solid black. The chromosome pair involved indicated by rods.

discovered were located in the X-chromosome. Certain females were encountered which gave daughters and sons in the ratio 2 : 1 instead of the normal 1 : 1 ratio.

This is due to the fact that the female in question carries a recessive lethal gene in one member of her X-chromosome pair (see Text-fig. 32). Its lethal effect

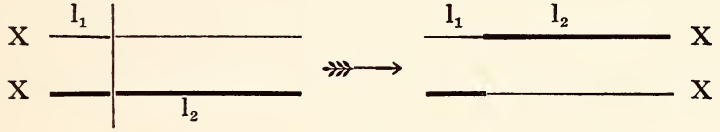
is overruled in the female by the opposite tendency of the normal allelomorph present in the other X-chromosome. But half of her sons which receive the lethal-bearing X are doomed since the Y-chromosome lacks the corresponding normal allelomorph.



32. Diagram showing inheritance of a sex-linked recessive lethal gene in Drosophila. The X-chromosome carrying the lethal gene (l) shown in outline, the other X with the dominant allelomorph in solid black. The hook-shaped Y-chromosome in dotted outline. Half of the sons will receive the lethal-carrying X-chromosome and die. (In parenthesis is indicated the situation if the sex-linked lethal induces the development of pigmented tumors in the larvae.)

By aid of their linkage to other sex-linked genes their map locus can be determined just as well as the locus of any other mutant gene. If in such a lethal-

bearing female a second lethal gene arises by mutation in the opposite X-chromosome, then all non-crossover sons will die. Among the crossover sons one-half will as a result of the crossing over receive both the lethal genes and accordingly die. The other half will get rid of both lethals and therefore survive. If the two lethals are close together crossing over will be rare so that only very few sons survive, a fact which accounts for cases in which particular females practically produce daughters only.



In different domesticated animals a number of lethal genes have also been encountered, but here the *sub-lethal* cases are most easily detected, cases in which the homozygous individuals are born alive, but die immediately after birth. As an illustration dominant white spotting in mice may be quoted, studied by Little, Detlefsen, and others. As shown by de Aberle, the individuals which are homozygous for this coat color gene are small and weak at birth and die soon after from a pronounced anemia. Their number of red blood corpuscles is only 14% of the normal.

By repeated injections of normal blood Gowen and

Gay were able to compensate this genotypical deficiency and keep the otherwise doomed individuals alive. It may be mentioned in this connection that an analogous therapeutic procedure has been successfully applied by P. E. Smith and MacDowell in a non-lethal case, viz., hereditary dwarfism in mice. Here pituitary transplants resulted in resumption of growth and normal function of the thyroid and adrenal glands which in the dwarfs showed abnormalities due to pituitary deficiency. These cases are interesting from a medical point of view, since they illustrate how genotypic pathological conditions may be alleviated by replacement of the deficiency from the environment.

In cattle we know a dominant gene which in heterozygous condition causes a shortening of the legs. In 1890 this gene was chosen as the standard factor of the short-legged Dexter breed. When inbred these Dexters give normal-legged individuals, standard short-legged Dexter individuals and still-born achondroplastic "bulldog" abortions (Plate VI, Fig. 24) in the ratio 1 : 2 : 1. The latter are homozygous for the dominant gene which in single dose causes the shortening of the legs. This gene has in other words a recessive lethal effect. Crew has presented evidence to the effect that the underlying cause is here a hereditary dysfunction of the pituitary gland, the hypophysis.

A related, less extreme recessive case has been studied in the Norwegian Telemark breed by the late Mr. Wriedt and the author. The homozygous bulldog calves which are here born alive are intelligent individuals, recalling the court jester type of human dwarfs now seen in the circuses (Plate VI, Fig. 25). In man there are incompletely dominant as well as recessive cases of a similar dwarfism known as *achondroplasia* (or *chondrodystrophy*) in which arms and legs are much shortened and the face has peculiar concave profile. In cattle the affected individuals die within a few days from respiratory paralysis, the diaphragm being overworked by the inability of these bulldog calves to stand up.

A series of recessive, mostly sub-lethal genes in cattle has been studied in Norway and Sweden by the same authors. One such causes lethal *congenital contractures* (Plate VII, Fig. 26), which frequently interfere with normal delivery; another induces a severe deformity and complete *anchylosis of the lower jaw* (Plate VII, Fig. 27). Other clear-cut recessives are *congenital hairlessness* (Plate VII, Fig. 28), the striking abnormalities found in the so-called *"elk-calves"* (Plate VII, Fig. 29) and in the *"amputated calves"* shown in Plate VII, Fig. 30. In the latter an almost total lack of a lower jaw gives the head a very peculiar parrot-like

appearance. The extreme reduction of the skeleton of the legs is due to an amalgamation and fusion of adjacent osseous rudiments during early embryonic life. In the "elk-calves" an analogous malformation affects the spinal column and the ribs in an elective way, parts which in the amputated calves are entirely unaffected. The shortened spinal column in combination with the normal head and the normal legs gives the "elk-calves" an appearance that may well account for the popular belief occasionally met with, viz., that these calves are due to crossing between a domestic cow and an elk bull.

In all these cases from Norway and Sweden, particular districts or even almost the entire breed in question have now been riddled with one or the other of these deleterious genes, owing to the fact that some prominent and highly prized sires were heterozygous for one of these recessive genes. When inbreeding is carried out among the offspring of these perfectly normal-looking bulls the malformed lethal homozygotes occur in the expected Mendelian ratios.

A striking illustration of the importance of the great sires in this respect may be derived from a survey of the 23 bull lines contained in the family herd book of Swedish Holstein-Friesians. Almost two-thirds of all the 900 bulls registered are descended from two im-

ported great sires, Gallus and Prins Adolf. It has been possible to demonstrate that one of these bulls carried the gene which produces the amputated calves, while the other was heterozygous for the gene for lethal congenital hairlessness.

A corresponding case has been described in horses by Jamane, involving a recessive gene which in homozygous condition induces *atresia coli,* the large intestine being completely cut off in the region of its pelvic flexure. This very undesirable gene was introduced into Japan from Ohio through a heterozygous Percheron stallion carrying the ironical name Superb, and has now become widespread in the entire district of Hokkaido.

From the very frequent occurrence of lethal and sublethal genes in all other organisms it is by analogy to be expected that they should be found also in human material. As a matter of fact, because of the prevailing cross-breeding habits of man there is every reason to believe that such genes have become relatively widespread in the human race.

We have seen earlier, (p. 60), how a first cousin marriage among two heterozygous short-fingered individuals gave rise to a badly deformed inviable cripple, presumably homozygous for the dominant gene which

in single dose affects the fingers and toes only. We have also discussed the non-existence of females homozygous for the recessive sex-linked gene for hæmophilia (cf. p. 74).

As a striking illustration of a recessive sub-lethal skin anomaly in man, *ichthyosis congenita,* form *typica* may be cited, in which an enormous hyperceratosis changes the skin into a leathery mail with red, bleeding fissures (Plate VII, Fig. 31). The majority of the homozygotes die *in utero,* the rest within a few days after delivery because of the inability of the skin to meet the demands of extra-uterine life. An interesting pedigree, almost an experiment in human material, has been published by Claus. A normal woman gave birth to five normal children by her husband. After his death she gave birth to three illegitimate children, all stillborn, ichthyotic individuals. It later turned out that the father of these children, although she did not know it, was her own half-brother from the same father.

Other genes with sub-lethal effects are the recessives *Xeroderma pigmentosum* and *infantile amaurotic idiocy,* Tay-Sachs. In the latter the ectodermal components of the central nervous system degenerate while the mesodermal parts are unaffected. Both these anomalies have been discussed in other connections. Other sub-lethal lesions are represented by the reces-

sive types of *glioma retinæ,* eye tumors which develop either *in utero* or during early childhood and which, without radical operation, invariably lead to death; the recessive genes for *spinal progressive muscular atrophy,* a congenital paralysis called Werdnig-Hofmann's disease; and for congenital types of *osteogenesis imperfecta,* characterized by an extraordinary brittleness of bones which leads to multiple fractures *in utero* (cf. Plate VIII, Fig. 32).

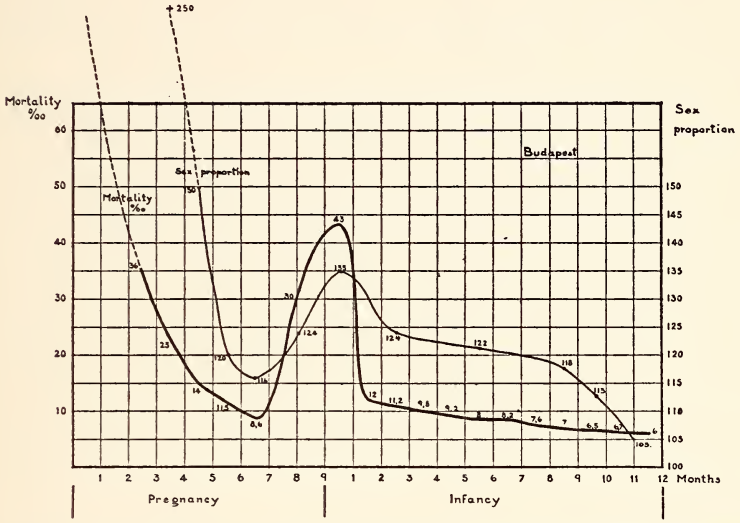
No doubt also a great many of the congenital malformations in pathological and anatomical collections, that were formerly quite vaguely attributed to strings or adhesions, arising from contact between the embryo and the internal embryonic membrane (amniotic adhesions) are in reality due to lethal genes. In Plate VIII, Fig. 33, a case is presented from the author's own experience which in several respects recalls the "amputated" calves. This malformed abortion was sent in to the Anatomical Institute of the University of Oslo more than ten years ago. When the information contained in the accompanying letter was later checked, it turned out that the parents were first cousins, a fact that strongly suggests that the malformation was due to a recessive lethal gene for which both parents had been heterozygous. In all analogous cases the possible

relationship of the parents should be thoroughly investigated.

A special point should also be briefly mentioned in this connection. We showed earlier, (p. 41) that as a result of the sex determination mechanism we expect males and females to be born in equal numbers, in man, for instance, 100 girls: 100 boys. Mass statistics, however, show a deviation from this expectation, viz., 106 boys: 100 girls, a distinct preponderance of boys.

And if we examine the sex of abortions and still-born individuals, this numerical preponderance of the male sex is still more pronounced. Thus Wedervang, after a critical treatment of very extensive statistical material, arrives at the conclusion that the sex ratio at fertilization, "the primary sex ratio," is in man probably even higher than 150 boys: 100 girls (see Text-fig. 33). This striking deviation from the theoretically expected sex ratio has generally been accounted for by the assumption that slight differences —probably in size—between the female-determining X-sperms and the male-determining Y-sperms give the latter an advantage in the competition during their swimming trip up through the uterus and the tubes towards the egg cell. If this is the case a relatively larger number of male embryos would be the result.

But recent experimental evidence on the sperm movements in mammals that has been obtained by Parker seems not to confirm this interpretation, so the question cannot yet be regarded as settled.



33. Curves demonstrating the sex proportion (number of boys : number of girls) and the mortality (‰) of children who died during pregnancy or infancy. FROM WEDERVANG.

However this may be, the question which in the *present* connection is of primary interest is the following: what is the cause of the preferential elimination or dying off of male embryos during pregnancy, a selective elimination that also continues during infancy?

The rise of the mortality curves before and during delivery, (cf. Text-fig. 33), may be accounted for by the

larger size of the male embryos, since the larger male embryos are more exposed to lesions during parturition. But this does not explain the fact that the preferential elimination of males is even more pronounced during the *early* months of pregnancy, i.e., at a time when size differences can be of no importance.

Weinberg, Lenz, and others have suggested that lethal and sub-lethal sex-linked genes which in the male have no normal allelomorphs are responsible for this remarkable selective elimination of males during pregnancy and infancy, and on the whole the evidence at hand seemed to be in accordance with this conception. But a serious complication recently arose when Landauer found that an analogous selective elimination of male embryos is also present in the fowl. Since in the fowl the males are XX and the females XY, we would on the above hypothesis expect that the females would here be preferentially eliminated. But the opposite is true. In view of this contradiction, the latter question also must so far be considered unsettled.

We have seen in how many ways the genes may interfere with normal development and viability: through alteration of a special germinal layer, a vital organ or a physiological or developmental process. And one might easily from such a review get the false

impression that almost any gene induces pathological states.

But if we have grasped the basic principle of Mendelian inheritance, we will realize that *for every gene which causes abnormalities or has a fatal effect, we must assume a corresponding normal allelomorph which is indispensable for the normal development of the character in question,* and even for survival itself. From this point of view the study of the numerous hereditary pathological traits and lethal cases makes us realize that a very large number of normal, vital genes are necessary for the normal development and maintenance of any organism.

That numerous factors may have a lethal effect is not surprising. What is *really* astonishing is the fact that the coöperation of this multitude of genes is generally so perfect that the very complicated embryological development and the interlocking physiological processes take a *normal* course, so that as a rule normal, viable individuals are produced.

3. HEREDITARY DISEASE CONDITIONS AS REVEALED BY TWIN INVESTIGATIONS

We have so far concentrated our attention on disease conditions attributable to a single factor difference. From experimental genetics we know that many such

characters are due to the coöperation of more than one gene. But in human material the interpretation of such cases is so difficult that reliable conclusions are generally excluded.

Under these circumstances the comparative study of twins, first introduced by Galton, represents a very important enrichment of the technique which in the hands of Siemens, Newman, v. Verschuer, Dahlberg, and many others has during recent years attained an ever increasing importance. More than five thousand pairs of twins have now been examined.

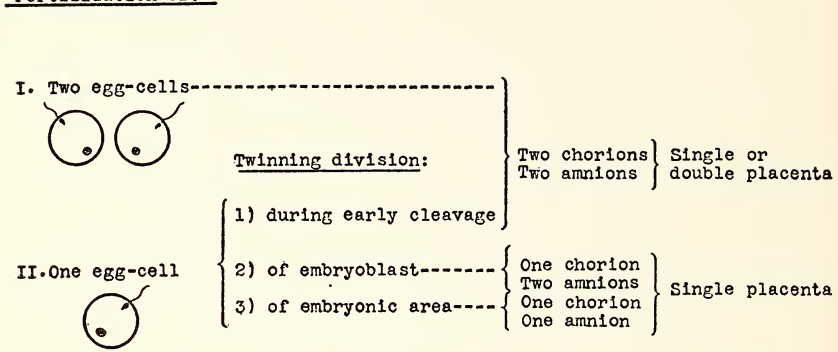
As is well known, there exist two fundamentally different types of human twins, the *dizygotic* or *fraternal twins* which simply represent a litter of two, and the *monozygotic* or *identical twins* which represent one biological individual in two parts. Dizygotic twins arise from two separate egg cells which have been fertilized by two different sperms; monozygotic twins are derived from one and the same fertilized egg cell which after fertilization has divided so that two zygotes are formed from one egg. These monozygotic twins are of identical genotype and accordingly strikingly alike and always of the same sex. The dizygotic twins, on the other hand, are not more like each other than are ordinary brothers and sisters, and like them may be of the same or of opposite sex.

The identical twins represent the final step in the series of partially double forms which, if the twinning division is incomplete, lead through the viable *conjoined* or *Siamese twins* (Plate VIII, Fig. 34) to the inviable *double monsters* of varying types and degrees (Plate VIII, Fig. 35). Probably because of the later onset of the incomplete division leading to conjoined twins, at a time when the bilateral asymmetry of the embryo has already partly been established, the paradoxical situation results that Siamese twins are *less* like each other than are free fraternal twins (Newman), (Plate IX, Fig. 36).

Recent systematic investigations of Curtius, Lassen, v. Verschuer, and others, have demonstrated beyond doubt that the condition of the egg sheaths or fœtal membranes does *not,* as previously assumed, represent a reliable basis for a separation between identical and fraternal twins. If in the case of identical twins the twinning division occurs during early cleavage, separate chorions and amnions (i.e., outer and inner egg membranes) may develop. If it occurs later, during the trophoblast and inner cell mass stage, a common chorion and two separate amnions may be formed, and if still later the twins may have the external and the internal membrane in common (see Text-fig. 34).

Under these conditions the so-called *polysomatic*

diagnosis of similarity, first developed by Siemens, represents the only reliable basis of classification. This diagnosis rests on a systematic comparison of a large number of characteristics which are variable in the population, such as blood groups, papillary patterns, type of hair, of eyebrows, nose, lips, ears, furrowing



34. Scheme representing the conditions of the egg sheaths (fœtal membranes) and the placenta in fraternal (I.) and identical (II.) twins.

of tongue, and skin vessels, as well as anthropological measurements and psychological tests. A crucial demonstration of the reliability of this method was afforded when Schiff in examining 446 pairs of twins found 202 pairs, which previously, and without Schiff's knowledge, had been diagnosed as monozygotic by v. Verschuer, using the polysomatic method. Schiff found in all these pairs that both members belonged to the

same blood group and had the same M-N factor combinations, thus independently confirming a diagnosis based on external features.

Clearly, variations which fall within the normal range of asymmetry exhibited by the two body halves are to be expected in identical co-twins also. But their striking similarity in all fundamental respects leaps to the eye. Thus, Bauer in operating upon a pair of identical twins with syndactyly (Plate IX, Fig. 37) was able to carry out successfully homoioplastic transplantation of skin, i.e., transplantation of skin from one individual to another, an operation that is otherwise impossible in man.

The question as to the hereditary mechanism behind the tendency to twin births prevailing in certain families can hardly as yet be regarded as settled. But for our purpose the following points are of primary interest: If a particular normal or pathological trait shows concordancy, i.e., if it is present in both members of a pair of identical co-twins, but shows discordancy in fraternal twins, this represents very strong evidence in favor of the trait being hereditary. Here the twin investigations carry us a step further than the pedigree investigations, since by this means more complicated cases, e.g., those which are due to more than one gene, may be recognized as being hereditary.

Furthermore, the twin investigations offer a unique opportunity for a determination of the *relative potency of heredity and environment,* "nature and nurture" in bringing about a particular character. Differences in the degree of age at onset of a particular hereditary alteration in the two members of a pair of identical twins is an indicator of the modifying influence of the environmental, "peristatic" forces. These external influences are already active *in utero,* for example, differences in blood supply, position, and so on. But clearly their modifying effect is still more marked after birth, in the form of differences in diseases, nourishment, training, etc., especially if the twins are reared apart. But since fraternal twins of the same sex are in this respect in the same position as are identical twins, they afford an ideal, and in more complicated cases, an indispensable control material. Hence, the modern twin investigations aim at the determination of concordancy and discordancy with respect to the pathological trait investigated, both in identical and in fraternal twins.

Some examples from the steadily increasing data may serve as illustrations. Several of these have kindly been placed at the author's disposal by v. Verschuer. In Plate IX, Fig. 38, a case of *inguinal hernia* in identical twins is represented. Such striking *mirror imaging*

is a phenomenon frequently encountered in identical twins; lefthandedness or even *situs inversus viscerum* in one of the co-twins having repeatedly been described. In the remarkable case presented in Plate X, Fig. 39, the gene must be very variable in its effect since one leg is normal while in the other a pronounced malformation of the foot is combined with almost complete absence of the leg. Parallels may be quoted from other malformations of the extremities as for instance polydactyly in which one hand may be perfectly normal while the other is entirely deformed. In such cases the environmental influences in prenatal life are clearly of very pronounced effect.

In the field of *dermatology,* skin diseases, the twin investigations of Siemens and others have revealed the hereditary component in the etiology of the skin eruption known as *acne,* of freckles, *cerrathosis pilaris* and a number of other anomalies; in *odontology* (Korkhaus) they have proved that time of dentition, type of implantation and even disposition to dental caries or decay are largely due to hereditary influences. In *ophthalmology* they have demonstrated that refraction anomalies, *myopy* and *hypermetropy,* are largely hereditary and have provided valuable information on the range of variation for the different types. The twin investigations have further shown that the type of

manifestation of the hereditary tendency to dislocation or *luxatio coxæ* and to *harelip* is very much dependent upon environmental influences, and that there is a clear hereditary element involved in the occurrence of *goitre* (see Plate X, Fig. 40). This falls into line with the well known fact that in the so-called "goitre belts" certain individuals are immune, while conversely sporadic goitre may occur in families living on the sea coast where iodine is abundant. Clearly, in the etiology of goitre two components coöperate, a hereditary inefficiency of the thyroid on one hand, a noxious environment on the other. Macklin has collected from the literature 10 pairs of identical twins in which both members developed *diabetes mellitus,* in 5 of the cases at practically the same age.

These scattered examples might easily be supplemented by other cases from different fields of pathology. But let us instead consider some outstanding *psychiatric twin investigations.* Luxenburger found that in identical twins both co-twins were *schizophrenic* in 52 cases, only one of them in 11 cases; while in fraternal twins the corresponding numbers were 3 and 47. Correspondingly for *manic-depressive* cases there was concordancy in 31, discordancy in 2 pairs of identical twins, while in fraternal twins of the same sex the numbers were 1 and 13 respectively.

The predominating, though not absolute influence of the genotype is quite apparent.

In schizophrenia, the form of insanity from which three-quarters of our insane asylum inmates are suffering, there were considerable variations both as regards type and onset among the two affected identical co-twins, a clear indication of the modifying influence of the environmental forces. In the manic-depressive co-twins the parallelism in type was greater on the whole. Of principal importance, however, is the fact that not infrequently one twin was predominantly manic, the other melancholic, a fact that coincides with the clinical conclusion that the two conditions are both expressions of one and the same basic disturbance.

Analogous investigations of *feeblemindedness* by J. C. Smith gave concordancy in 11, discordancy in 2 pairs of identical twins, while the corresponding numbers for fraternal twins were 4 and 46, respectively (see Plate X, Fig. 41 and Plate XI, Fig. 42). Hence, it is apparent that different types of feeblemindedness are to a marked extent genotypically determined, a result which falls into line with evidence from pedigree investigations presented by Goddard. The same holds true of *epilepsy;* according to Sanders there was concordancy in 16, discordancy in 7 pairs of identical

twins, while the corresponding numbers for fraternal twins were 2 and 15 respectively.

Finally Lange in his twin analysis of *criminality* found that in 10 cases of identical twins both co-twins had a criminal record, while in 3 cases only one co-twin had been sentenced. Conversely, in fraternal twins there was concordancy only in 2 cases, discordancy in 15. Though the numbers are too small and the diagnosis of criminality very vague, it can hardly be denied that a hereditary weakness of character favors the development of an asocial behavior, a result which on the whole seems natural in view of Muller's and especially Newman's evidence on the intelligence and temperament of identical twins reared apart. In more extensive material studied by Kranz the difference between identical and fraternal twins (of same sex) with respect to "criminality" was distinctly less marked. In the former concordancy was present in 17, discordancy in 10 cases; among the latter concordancy in 18, discordancy in 19 cases. Both as regards schizophrenia, manic-depressive psychoses and criminality the results of Dutch twin investigations of Legras are in accordance with those presented above.

As a last example of twin investigations Diehl's and v. Verschuer's recent monograph on *tuberculosis* in twins may be mentioned, an investigation in which

both the clinical type and the environmental conditions were determined as far as possible. In a total of 37 pairs of identical twins both co-twins had developed tuberculosis in 26 pairs; only one of them in 11 pairs. Conversely, among 69 pairs of fraternal twins concordancy with respect to tuberculosis was present in 17, discordancy in 52 cases. Among 9 pairs in which—in spite of quite similar exposure to infection—only one co-twin was affected, 8 pairs were fraternal and only 1 pair identical twins. Conversely, among 7 pairs in which both members were affected in spite of no known exposure, 5 pairs were identical, and 2 fraternal. Even the clinical type was in some cases strikingly similar. An extremely remarkable case was found in which two identical twin brothers, within a time interval of four years, both developed a surgical tuberculosis in the heel bone!

On the whole the evidence from tuberculosis in twins gives the old vague notion of constitutional disposition to tuberculosis a solid and more definite basis. It is clear that the capriciousness seen in the occurrence of tuberculosis is to some extent due to differences in the genotypes on which the environmental agencies, in this case, the bacilli, act.

4. INTERSEXUALITY AND SEX REVERSAL. PSEUDO-HERMAPHRODITISM IN MAN

In the foregoing we have endeavored to familiarize ourselves with the genes and the mechanism of their distribution, and we have seen what a prominent part they play in bringing about disease conditions. But we have heard very little so far about *how* they exert their action.

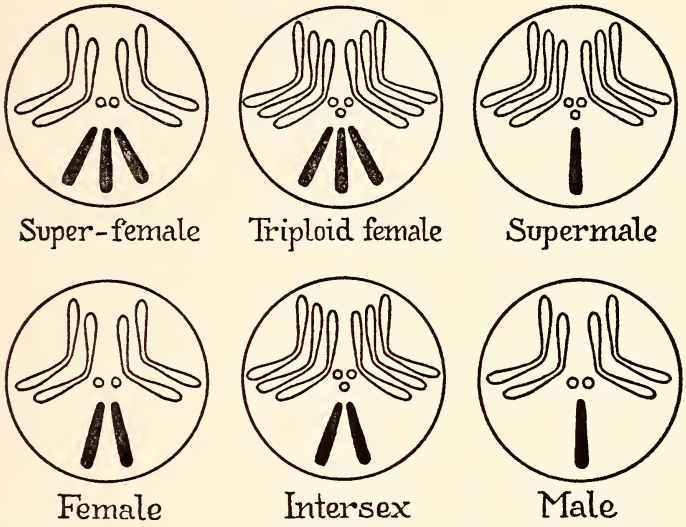
A certain insight into this question may be derived from a consideration of the genotypical mechanism which lies behind the phenomenon of intersexuality, a condition which also attracts our interest from the point of view of general medicine.

We recall how the *primary* sex determination of an individual depends upon the alternative combination of sex chromosomes at fertilization, XX giving a female, XY a male (cf. p. 38 and Text-fig. 5).

But this is not the whole story.

In a particular Drosophila cross Bridges obtained 96 females, 9 males and 80 sterile individuals which both as regards body and sex glands were complex mixtures of male and female parts, so-called intersexes. By genetic and cytological analysis Bridges proved that these exceptional individuals had three full sets of autosomes, but only two X-chromosomes.

If we denote one set of autosomes by A, they were accordingly 2X 3A individuals. Ordinary 1X 2A individuals are males, 2X 2A individuals are females. Since the addition of one set of autosomes turns the scale towards maleness (in the intersexes) Bridges con-



35. Effect on sex of the balance between X-chromosomes (black) and autosomes (outlined) in Drosophila. The Y-chromosome disregarded. AFTER SINNOTT AND DUNN.

cluded that the autosomes also must contain sex-determining genes, and these genes must have a net *male* effect, while conversely the X-chromosome contains sex differentiators with a net *female* tendency.

Sex is accordingly not a function of the sex chromosomes alone. It must be a matter of the correct

quantitative balance between the number of male- and female-determining genes. Further, the net male tendency of one set of autosomes must be less potent than the net female tendency of an X, since in ordinary 2X 2A individuals the female tendency gains the upper hand, resulting in the formation of a normal female.

TABLE I. *Sexual types in Drosophila (after Bridges)*

Sex	Number of X-chromosomes	Sets of autosomes (A)	Sex index (X/A ratio)
Superfemale	3	2	1,5
Normal female { tetraploid	4	4	1,0
Normal female { triploid ..	3	3	1,0
Normal female { diploid ..	2	2	1,0
Intersex	2	3	0,67
Normal male	1	2	0,50
Supermale	1	3	0,33

The correctness of this balance conception was confirmed when Bridges also found that 4X 2A individuals, and 1X 3A individuals showed striking abnormalities which justified the designations superfemales and supermales given to these types, while on the other hand the triploid 3X 3A, or the tetraploid 4X 4A individuals were normal females, since here

the ratio is like that of ordinary 2X 2A females. The chromosome equipment and the sex indices of these types are presented in Text-fig. 35 and Table I respectively.

The outstanding importance of this brilliant work lies in the actual demonstration of the chromosome aberrations leading to deviations from the normal male and female balance. The basic conception that sex is the result of a balance, a competition so to speak, between two opposite tendencies, and that each sex contains male-determining and female-determining genes in a particular quantitative ratio had considerably earlier been elaborated by Goldschmidt in his famous experiments with the gypsy moth.

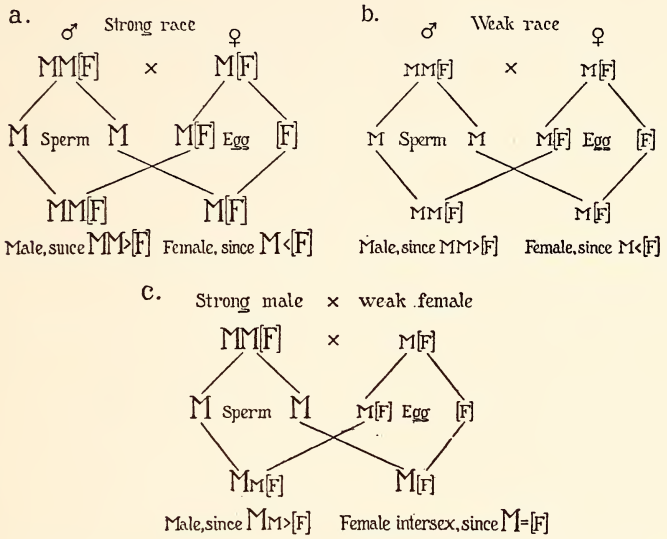
If European specimens of this moth (*Lymantria dispar*) are bred among themselves, males and females are obtained in equal numbers. The same is true of the Japanese variety, *Lymantria Japonica.* But if a Japanese male is mated to a European female the sons are normal, but the potential daughters show an admixture of typically male features; they are female intersexes. The reciprocal cross produces normal offspring in the first generation. But if these F_1 animals are inbred, a certain proportion of males with an admixture of female characteristics, i.e., male intersexes, appear.

Further, when different sub-races of European and Japanese moths were crossed, it turned out that the *degree* of intersexuality was definite for each particular mating. Goldschmidt denotes the different varieties as relatively "weak" or "strong." Thus, for instance, a strong male when mated to a weak female will give about 50% of normal males and 50% of female intersexes, while a very strong male by a weak female will give offspring all male. By appropriate matings it was thus possible to produce every stage in the transition of potential females into males, and conversely (see Plate XI, Fig. 43 and Fig. 44).

Goldschmidt accounts for these remarkable results by introducing a quantitative notion of potency distinguishing the sex-determining genes of the different sub-races. The potency governs the rate at which the respective sex-determining substances are produced. In moths the males are XX, the females XY. From particular experiments Goldschmidt concludes that in this form the X contains a male-determining gene M, whereas the female-determining factor is controlled by the cytoplasm of the egg. All the eggs will accordingly contain the female tendency (in Text-figs. 36 and 37 indicated by brackets), but only half of them, the X eggs, will in addition have a male gene. All the sperms,

on the other hand, will contain the male-determining gene since each sperm transmits an X-chromosome.

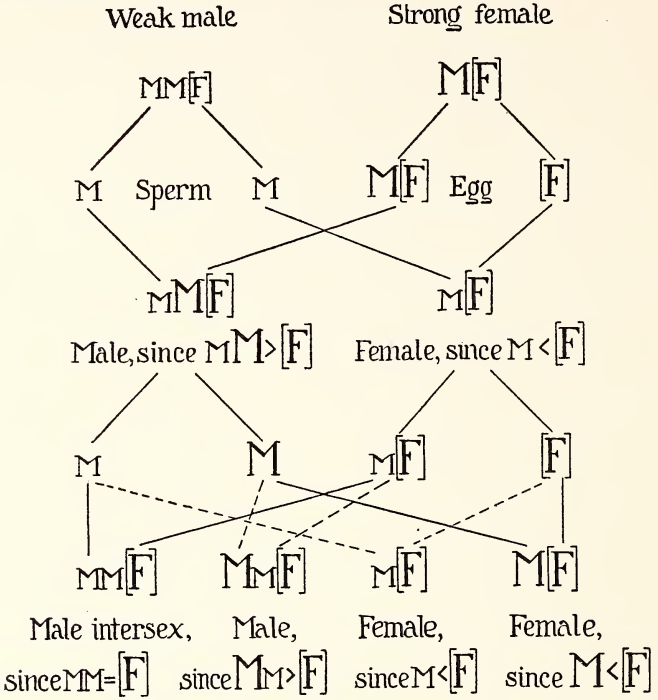
In the diagram, Text-fig. 36, the strong and weak sex factors are denoted by letters of different size. In the



36. Diagram to illustrate the result of Lymantria matings. The "strong" and "weak" sex factors indicated by letters of different size. M, gene for maleness; F, factor for femaleness in the egg cytoplasm (indicated by brackets). a., strong male × strong female; b., weak male × weak female; c., strong male × weak female.

matings *a* and *b*, females and males will be obtained in equal numbers, since in one and the same race two M's always overrule one F giving maleness, while F overrules a single M, resulting in femaleness. But in mating *c* of a strong male with weak female the sons

will be normal, since strong *M* plus weak *m* overrule the weak *f*-tendency, while the potential females will be intersexes, since the strong *M* keeps the weak *f* in balance.



37. The results of crossing a weak Lymantria male × strong female, and inbreeding the offspring. Symbols as in Text-fig. 36.

Weak male by strong female (Text-fig. 37) gives normal males and females, since strong *M* plus weak *m* overrule strong *F*, and strong *F* overrules weak *m*. But if these moths are inbred, half of the expected

sons will be male intersexes, since strong *F* keeps two weak *M*'s in balance.

The main conclusion derived from these and other experiments may be summarized thus: *Each sex possesses the potentialities of the other, since each can become intersexual.* In every individual there is a competition between male-determining and female-determining tendencies due to formative substances discharged from the respective genes.

In the normal XX or XY individuals one or the other of these substances is effectively in excess over its opponent during the entire development. But if, owing to chromosome aberrations or to mutations in the sex genes, this normal balance is upset, the rate of production of the respective sex-differentiating substance will be altered. Then the individual will start its development as a male (or female) up to a certain point, when the opposite substances will be actively in excess and gain the upper hand. From this point the structures of the sexual organization which have not completed their development will continue their differentiation according to the pattern of the opposite sex. Hence the organs which are first developed are the last to be modified, and conversely. *The intersexes are in other words mosaics in time,* the degree of inter-

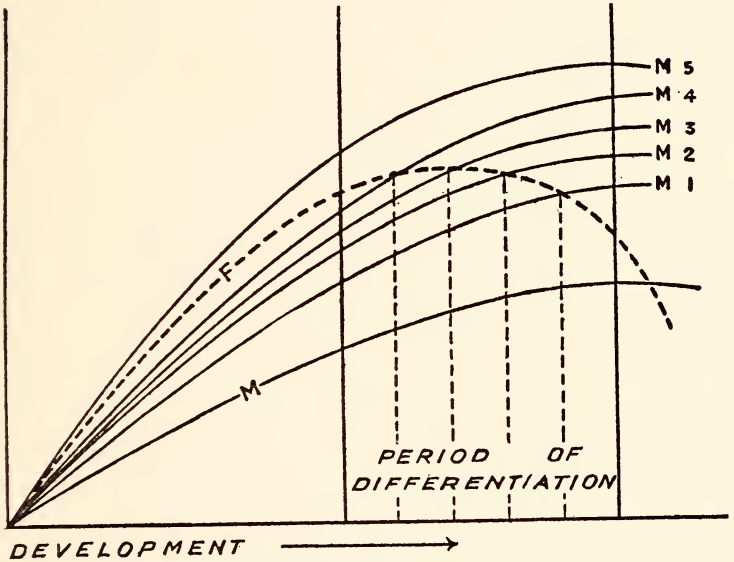
sexuality being determined by the time at which this switch-over occurs.

38. Section through the ovary of an intersexual Lymantria female. Female germ cells changing into sperm. To the right, egg cells and sperm in the same tubes. FROM GOLDSCHMIDT.

An illustration is shown in the diagram, Text-fig. 38, which represents a section through an ovary from a female intersex, with eggs and sperms lying together in one and the same cyst.

In the diagram, Text-fig. 39, the imaginary curves illustrate F, the rate at which female-determining, M, the rate at which male-determining substances are set free. The FM combination results in femaleness, since

here F is all the time actively in excess. But in those cases where the same F through crossing is combined with M's of greater potency (from other races) in the order $M_{1\,5}$, a switch-over will occur later (M_1) or sooner (M_4) during development, resulting in the production of different steps of female intersexuality up to complete sex reversal (M_5).



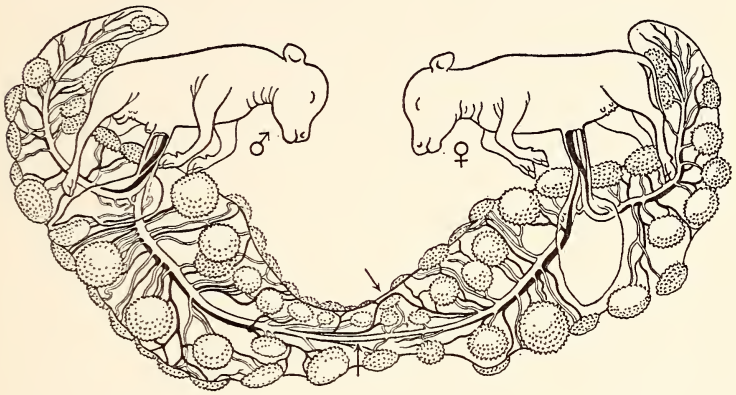
39. Diagrammatic representation of the relative rates of production of female-determining (F) and male-determining (M) substances in cases of female intersexuality. The FM combination gives normal female. When the same F is combined with M's of greater potency (in the order M_1-M_4) a switch-over will occur sooner (M_4) or later (M_1) during embryonic development, resulting in female intersexuality of different degree. The FM_5 combination gives complete sex reversal. AFTER GOLDSCHMIDT FROM CREW.

In the *higher animals* in which hormones or ductless gland secretions are active the chromosomal *sex determination* mechanism is the same, but here the situation is complicated by the fact that the later *sex differentiation* is taken over by extra-cellular products, the sex hormones. That the primary, genotypic XX—XY balance may here be overridden by abnormalities in the production of the sex hormones is evident both from a series of transplantation and parabiosis experiments and particularly strikingly illustrated by one of nature's own experiments.

In cattle it sometimes happens that a pair of twins is born, of which one is a normal male, while the other is a sterile individual with abnormal genital organs, a so-called *free-martin*. As shown by Tandler and Keller, and by Lillie, this bovine free-martin with preponderantly female external genitalia and the internal genitalia more or less male, is an XX, i.e., female co-twin to the normal male calf. Due to vascular intercommunications in the fused egg membranes (Text-fig. 40) male sex hormones from the testes, which start their development earlier than the ovaries, will enter the blood circulation of the female co-twin and change her sex differentiation in a male direction.

Thus the hormone animals are also sexually bipotential, hermaphroditic at fertilization. The anlage

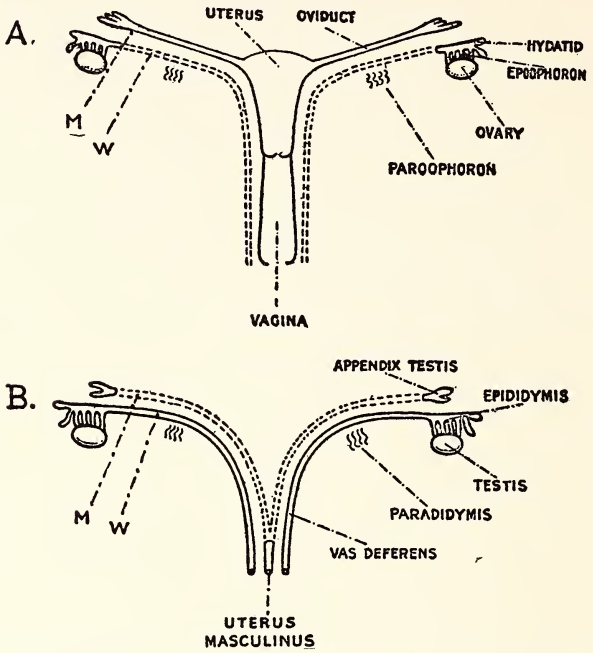
of two sets of sexual ducts, the Wolffian and Müllerian ducts, as well as the early identity of the external genitalia in both sexes is an expression of this relation. Each rudiment is capable of either male or female development.



40. Twin calves of opposite sex with vascular connections (indicated by arrows) in the fused embryonic envelopes. The calf to the right will become a free-martin. AFTER LILLIE.

In normal males, the Wolffian ducts develop, forming the permanent seminal ducts, while the Müllerian ducts degenerate, except for some slight traces which correspond embryologically to analogous structures of the opposite sex. Conversely in the females, the Müllerian ducts are retained and develop into the oviducts, the uterus and the vagina, while of the Wolffian ducts only some unimportant rudiments are left, (see Text-fig. 41). It is otherwise if the normal

genotypical balance is upset by mutations in the sex genes or by changes in the hormonal environment in which the gonads develop. Then intersexuality results.



41. Diagram illustrating the alternative development of the Wolffian (W) and the Müllerian (M) ducts in females (A) and males (B). Those parts that persist (as functional organs or as rudiments) are indicated in solid outlines, those parts that degenerate, in dotted outlines. AFTER BROMAN FROM CREW.

As indicated by Witchi's work in amphibians the fœtal hormones from the cortex of the aboriginally ambisexual gonad are inductors of female, those from the medulla of male sex differentiation. When, in the

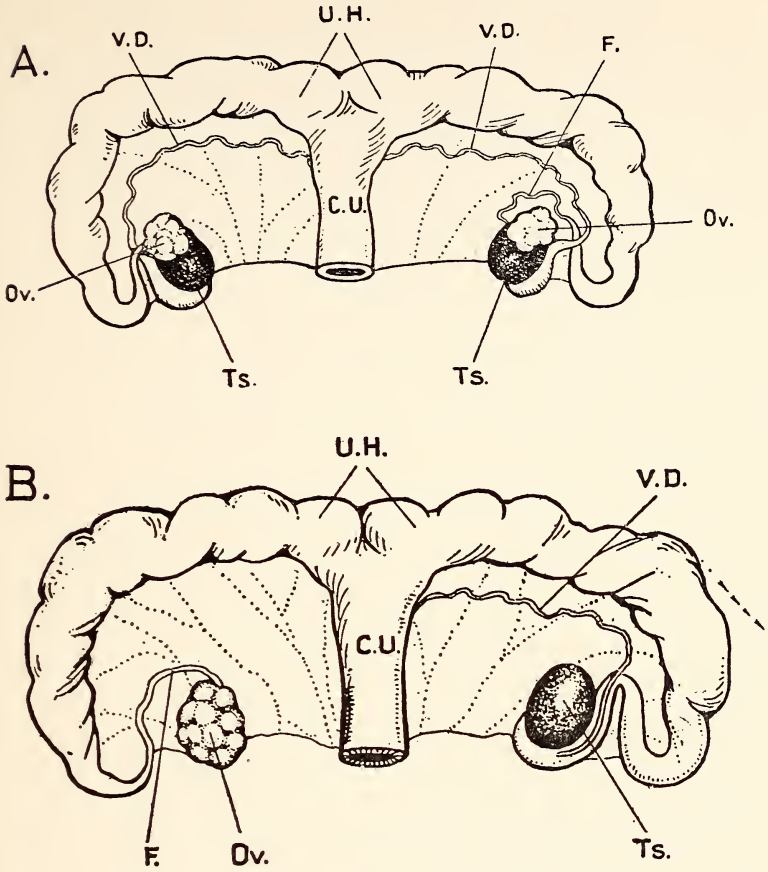
higher animals, the external covering of the testis, the *tunica albuginea,* has developed, no remnants of the cortex, the source of the female sex differentiating substance, are left. This relation interferes with the development of male intersexuality in higher animals, including man. It is otherwise in the female sex. The female also during later development possesses in the medullary component of the ovary a source of male hormones which under the above-mentioned atypical conditions may enter into an active phase. The possibility of intersexual development is therefore inherent in the female.

It should be emphasized that these fœtal, genetically controlled cortical or medullary hormones are not identical with the definitive sex-hormones which are later produced by the follicular apparatus of the ovary and the interstitial cells of the testis. These definitive sex hormones, the sexual hormones in the ordinary sense of the word, are not governed by the genes, but are simply dependent upon whether those cells which represent the source of these hormones have actually been formed and have entered into an active phase. As will be readily understood, this involves a further complication, which will have to be taken into account in the interpretation of the individual intersexuality cases encountered in higher animals and man.

The sex theory of Goldschmidt, which here is necessarily presented in almost hazardous condensation, comprises points which are as yet more or less hypothetical. But it has the great advantage of bringing under one consistent viewpoint a wide series of normal and pathological phenomena which seemed formerly very contradictory, as a matter of fact inexplicable.

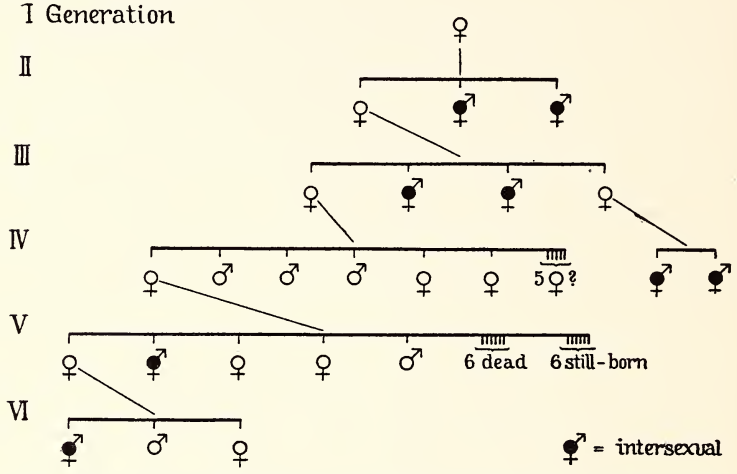
Thus the frequent *pseudo-hermaphroditism* encountered in mammals, especially in pigs (see Text-fig. 42), and goats where clear hereditary cases are known, such as the sacred pigs in the New Hebrides studied by Baker and the Toggenburger race of goats investigated by Krediet, is clearly due to female intersexuality.

The same is true of pseudo-hermaphroditism in man. Goldschmidt rejects the entire mélange of old morphological classifications as absolutely unbiological. The large majority of the more than 2,000 cases recorded are simply cases of female intersexuality of medium degree (see Plate XII, Fig. 45). The switch-over has occurred previous to the degeneration of the Wolffian ducts. The gonads exhibit different degrees of ovo-testis formation (see Plate XII, Fig. 46), the medullary part of the ovary having been transformed into testicular tissue, and remnants of the Wolffian ducts are present (Plate XII, Fig. 46A).



42. Internal genitalia from cases of female intersexuality in the pig. A, the ovaries transformed into ovo-testes; rudimentary sperm ducts on both sides. B., Ovary on the left, testis on the right side; sperm duct on right side only. C.U., uterine body; U.H., uterine horn; Ov., ovary; F., oviduct. Ts., testis; V.D., sperm duct. FROM CREW.

In quite a few cases where the switch-over has occurred early, spermatocytes and even sperms have been encountered (Martin, Dieffenbach, Merkels). If the switch-over occurs very early, then complete sex reversal is to be expected. Such a transformed XX male on mating to a normal XX female could produce daughters only.



43. Pedigree showing hereditary transmission of tendency to female intersexuality in man. ♂ female intersex of various degrees. AFTER DIEFFENBACH.

The frequent asymmetry of the malformations to which so much importance has been attributed in the old nomenclature is, as emphasized by Goldschmidt, of no principal importance. It is a direct consequence of slight differences in concentration of the differentiating hormones in different parts of the primordia

of the two body halves. Numerous parallels from monofactorial genetic characters have been presented earlier; polydactyly may serve as an example.

As clear *hereditary* cases of female intersexuality in man Dieffenbach's case may be quoted, of which a pedigree is presented in Text-fig. 43. Very striking also is Loennechen's case from Norway, in which three adult sisters, when operated upon for inguinal hernia, were found to have testis-like gonads, which in one case contained spermatogonia and spermatocytes. According to Goldschmidt two cases of intersexual identical twins are also on record. That the change may be genotypically determined, presumably due to mutation in one of the sex genes, is thus perfectly clear. As a parallel from experimental genetics a recessive mutant gene in *Drosophila simulans* may be quoted, studied by Sturtevant, which causes intersexuality though of a somewhat special type.

Male intersexuality has not been encountered in man, since in the male gonad no remnants are left of cortical components during later embryological development. And two particular pathological states which may cause confusion have nothing to do with intersexuality.

One of these is the so-called *virilism* in which women with normal female internal genitalia may

exhibit a hypospadic phallus and sometimes a scrotum-like structure. As emphasized by Berner these malformations are due to a hyperplastic tumor in the cortex of the suprarenal glands. This demonstrates that the male differentiation of the external genitalia is also influenced by adrenal hormones, presumably the same which induce *pubertas præcox,* premature development of secondary sexual characters, in small children.

The other pathological state to be kept apart from intersexuality is *hypospadia* pure and simple. Due to an inhibition of the normal closure of the groove which constitutes the anlage of the urethra, the latter will have an abnormal extra opening. Clear-cut dominant cases of this malformation are known in man. In Plate XII, Fig. 47, a pair of identical twins with hypospadia is presented.

For those who have been brought up in the old conception of sexuality the idea of *complete sex reversal* seems perhaps most difficult to accept. But it should be remembered that in nature quite a few lower forms, as for instance the oyster, practice normal sex reversal. And in amphibians and birds where the normal balance is less stable than in mammals, clear cases of complete sex reversal are known.

Thus, in 1921 Crew received a Buff-Orpington hen, previously mother to chickens, which had developed

spurs and started to crow. In 1922 she developed typically male feathering and a real comb (see Plate XII, Fig. 48), fought the cock and made courtship to her sister hens. When isolated with a virgin hen she mated repeatedly, after which her partner laid nine eggs from which two perfectly normal chickens hatched out. Shortly afterwards the hen-cock turned ill, and the 29th of December, 1922, she drowned herself in a pond, a tragical ending of a rather complicated career. In the abdomen there was a severe tuberculosis. The ovary was very rudimentary, and two small testes had developed, a situation which is in accordance with the experimental results of complete gonadectomy in the fowl, by Benoit, Sand, Domm and others, which demonstrate that when through the removal of the ovary the normal balance is upset, then preponderantly male gonad tissue regenerates.

5. GENES AND HORMONES

We know that the genes are physical particles located in the chromosomes. Certain calculations by Morgan, Muller and by Gowen and Gay give estimates for the size of the gene which fall within the order of magnitude of large organic molecules. These organic particles have the power of propagation and they in-

duce the development of all our hereditary characteristics.

While we have very extensive information on the mechanism of the distribution of the genes, very little is known about their real nature and mode of action in bringing about the final end result which we are primarily studying, i.e., the hereditary characters induced by the genes.

Goldschmidt regards the difference in potency of the sex genes just dealt with as an expression of a greater or smaller *quantity* of the same gene substance and applies this quantitative conception with proportional rates of reaction to the genes in general. The genes themselves are according to this view autocatalytic substances which, like the sex-differentiating hormones, exert their action on the respective primordia of the embryo, provided they are present in the right spot, at the right time and in a sufficient concentration, above a particular threshold of reaction.

The individual development is in this view a successive chain of such reactions properly governed by the genes. A mutation in a particular gene is a quantitative alteration in the amount of the particular gene substance, which by changing the reaction velocity leads to a modification of the corresponding character.

Though it is not apparent why a qualitative change

in the gene might not have similar effects, Goldschmidt's analysis of the physiological inter-relationship between genes and characters has introduced very interesting and fruitful viewpoints. His general view falls well into line with the evidence from Spemann's embryological experiments which indicate that the total embryological development of an individual comprises the establishment of a consecutive series of organizer-like induction territories which produce hormone-like substances. The reaction-velocity conception is supported by a wide series of results from experimental embryology, as for instance those of Stockard, which demonstrate that a change in the rate of development by temperature or different chemicals leads to gross embryological abnormalities.

That genes may act in much the same way is evidenced by different investigations. Thus, Dunn and Landauer have shown that the dominant gene for chondrodystrophy (achondroplasia) in the short-legged Creeper fowl, which kills the embryo in homozygous condition after about 72 hours of incubation, exerts this action by a very striking retardation of the development, the different parts of the embryo being affected in the order of their relative growth rates (see Plate XIII, Fig. 49). Occasionally some homozygotes live for somewhat longer periods, and

then lack hindlimbs and eyelids and exhibit gross eye abnormalities, e.g., microphthalmus and coloboma.

Stockard's demonstration of the fact that a retardation of the development frequently results in budding and twin formation possibly finds a parallel in the double-monster, Plate XIII, Fig. 50, which exhibits harelip, a malformation which is clearly due to a disturbance of the normal growth rate and the fusion of the face processes of the embryo. In the monster, Plate XIII, Fig. 51, harelip, polydactyly and brain hernia are combined, a series of anomalies which may all be attributed to developmental inhibition. We have seen earlier that harelip and polydactyly are malformations which may be induced by simple Mendelian genes.

That the genes may act much like hormones or may possibly regulate the production of hormones, is evidenced by the recent very interesting results of Lillie and his co-workers, Domm, Gustafson, Juhn and others. By fractional injection of female sex hormone in gonadectomized fowls it was thus possible to imitate strikingly in the growing feathers the barred character, which in the barred fowl is due to a distinct gene. This suggests that the genotypically determined barring is due to a rhythmical activity of the gene for barring, acting through graded thresholds of reaction

similar to those determined experimentally by injection of the sex hormone.

That endocrines in hormone animals may form an important link between genes and characters becomes daily clearer. When we encounter cases like the family with two homozygous recessive midgets presented in Plate XIV, Fig. 53, a pair of identical chondrodystrophic twins as that presented in Plate XIII, Fig. 52, or hereditary cases of *osteopsathyrosis* or of *adipositas* (Plate XIV, Figs. 54 and 55) we can hardly doubt that hereditary dysfunctions of the endocrine glands are involved.

Happily, a steadily increasing number of parallel mutations in domesticated and laboratory animals are accessible to experimental and embryological analysis. Numerous scientists, Landauer and Dunn, Stockard, P. E. Smith and MacDowell, Bonnevie, Bagg and many others are engaged in such investigations which it may be hoped will give us a more definite insight into the single steps in the pathogenetic processes leading to analogous states in man. There is no doubt that a systematic investigation of parallel cases in animals is the proper way of further progress in this field. In Stockard's laboratory I recently had an opportunity of seeing a large number of histological preparations from endocrine glands of dogs suffering from different

hereditary anomalies, which in numerous respects correspond to analogous abnormalities in human beings. In quite a few cases the endocrine glands showed striking microscopical alterations, typical for the pathological state exhibited by the dog in question. The illustrations derived from the frontispiece of a recent book of Stockard which are presented in Plate XIV, Fig. 56, and Plate XV, Fig. 57, are quite amusing, though we should be aware that in these cases we do not yet know to what extent the similarity is phenotypically determined.

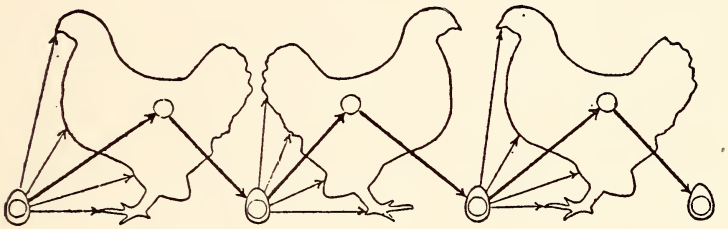
These scattered indications may suffice to give an impression of a new field where our notions are as yet rather vague, but where it may be hoped that future work may lead to results that are of considerable practical importance. We shall now consider another domain where the recent years have enriched our knowledge with clear-cut and extremely important evidence.

6. X-RAYS AND HEREDITY

Among the thousands of experiments which aimed at the demonstration of the inheritance of acquired characters, changes which affect the body in the course of life, not one has led to convincing affirmative results. The body is only a container within which the germ cells are protected and maintained. The child does not

inherit anything from the body of the parents, it receives only from their germ cells the chromosomes and the genes which these germ cells have received from the ancestors.

The situation may be made clear by aid of a diagram. The old conception that the egg produces a hen that again produces eggs which give rise to new hens is erroneous. The correct view is presented in Text-fig.



44. Diagram showing how the egg produces new eggs and, in addition, the body of the hen. The germ track indicated by heavier lines. FROM CONKLIN.

44: The egg produces new eggs plus a body that constitutes a protecting container for the eggs. The individual hen merely represents an intumescence on the continuous line of germ cells, the *germ track,* of the species. External influences, lesions, diseases, etc., that induce changes in the body do not penetrate deep enough to induce changes in the genes.

This high autonomy of the genes is strikingly illustrated by Castle's classical experiment in which the

ovaries from a pure dominant black guinea-pig were engrafted into an albino. This albino female when mated to a pure albino male produced black offspring only. Hence the germ cells retain their independence even though living in a body of foreign, and genotypically different, constitution.

However, as we know from the study of mutations, changes in the genes *do* occur, and they must have a cause. No wonder that, when the selective effect of the X-rays on the germ cells was detected, numerous workers tried to induce mutations by radiation. But if mutations eventually turned up in the X-rayed material there was no means of deciding whether these mutations were due to the treatment or had arisen spontaneously.

It is here that H. J. Muller's work inaugurates a new epoch. His great achievement is not primarily the artificial production of mutations, but the development of a *method* by which the normal, and the experimentally increased mutation frequency might be determined quantitatively. For this purpose he depended upon the lethal genes which represent, as we have heard, by far the most frequent type of mutation. In particular Drosophila crosses, especially devised for this purpose, he kept track of a particular chromosome and counted the lethals which arose in this chromosome, both under

ordinary conditions (in untreated control material), and after irradiation.

In order to illustrate the principles that lie behind the methods applied we may refer to the diagram of the attached-X stock, Text-fig. 21, p. 97. In matings of attached-X females, all the sons receive their X-chromosome directly from the father. Hence, if a lethal mutation has occurred in this X as a result of X-raying the father, all the sons will die so that the mating gives daughters only. Correspondingly, if the mutation is a sex-linked non-lethal mutation, it will manifest itself immediately in all the sons. By comparing the number of lethal and visible mutations in X-rayed and in untreated material we get a direct quantitative expression of the mutation frequency within the two lines.

The result of the X-ray treatment was striking. The mutation frequency was increased by several hundred per cent. In some experiments there appeared a new lethal in one out of every ten treated chromosomes. By X-raying eggs or larvæ somatic mutations occurred, resulting in the appearance of larger or smaller mosaic areas.

These radiation mutations are in every respect like and frequently identical with those of apparently spontaneous origin. The active principle is believed to be the electrons released by the short-wave high frequency

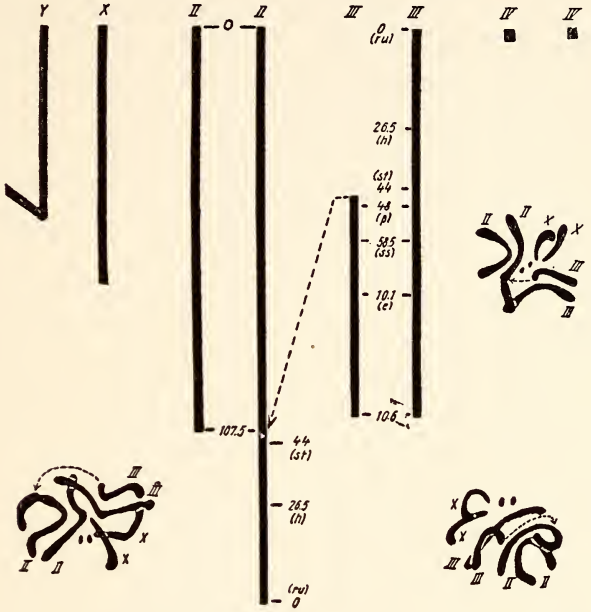
radiation, and, as shown by Hanson and by Stadler, the gamma rays and free electrons of radium act just as well. The mutation frequency is on the whole proportional to the quantity of radiation, that is, to the ionizing effect of the dosage applied. Ripe sperm cells are particularly sensitive.

In addition to changes in single genes (point mutations) changes in whole chromosomes or their parts have been induced which will open up important new fields of work in theoretical genetics. As an example of such changes we cite a case in which a section from the third chromosome in Drosophila has been translocated to the second and is plainly visible under the microscope (Text-fig. 45).

Within the few years that have passed since Muller's discovery, the general nature of this effect of radiation has already been conclusively established by analogous experiments in very different plants and animals, and we are fully justified in concluding that the same principle applies to human material as well.

This knowledge has important practical bearing. One must thus strongly advise against temporary sterilization of women by X-rays. The accidental temporary sterilization suffered by Roentgenologists due to faulty protection is also serious. It is true that different statistics (Loeffler, Pankow, and others) on the occurrence

of miscarriage and malformations among the children of parents whose gonads have been exposed to Roentgen treatment are not conclusive. As a matter of fact,



45. Chromosome translocation induced by X-rays in Drosophila. A large section from one member of the III chromosome pair has been translocated to one member of the II chromosome pair. The arrows show the point of break and the point of new attachment. The equatorial plates show just the change that had been predicted on basis of the experimental evidence that is summarized in the chromosome map above. AFTER PAINTER AND MULLER FROM TIMOFÉEFF-RESSOVSKY.

they *can* not be. The large majority of mutations are recessive. Only if a recessive mutation occurs in the X of a treated mother is there a possibility of its manifestation in some of her sons. If it occurs in the X of

a treated father it cannot manifest its presence except possibly in some of his daughter's sons. And if the mutation is autosomal, which—since we have 23 pairs of autosomes—is 23 times as likely, then it cannot manifest itself until the fourth generation, and then only if two grandchildren happen to marry. But having once arisen the mutant gene will nevertheless be transmitted to half of all the descending lines and may thus spread in the population. This is a serious situation when we remember that the large majority of mutations are unfavorable, leading to hereditary defects of different type and degree.

7. ALCOHOL AND HEREDITY

WHILE the evidence on the effect of radiation is clear and consistent the opposite is true of the data dealing with the alleged injurious hereditary effect of alcohol and other chemicals, lead, mercury, nicotine, etc.

The old, pre-Mendelian statistical analysis of human material is full of gross sources of error, and as regards the experimental work with alcoholization of different laboratory animals it may safely be stated that the evidence indicating that alcohol causes genotypical changes grows gradually weaker with the improvement of technique and a more critical attitude in the evaluation of the results. As late as 1930 Agnes Bluhm, who

herself believes alcohol to have a hereditary effect, expressed the opinion that practically all the earlier experiments suffer from the defect that the numbers of animals are too small and the selection of control material too uncritical.

To this is added the knowledge that the characters studied, such as fertility, sex ratio, and death rate, are very "poor" characters from a genetic point of view, and that in much of the earlier work no sharp distinction was drawn between the effect of alcoholization in males and females. Clearly a prolonged saturation of the blood with alcohol in pregnant females may well be expected to lower the fertility by giving the embryos an unfavorable environment, but this tells nothing about any *hereditary* influence.

The most thorough experiments, as those of Hanson and Heys, MacDowell and Lord, Gyllensvärd, Colin—the latter working with lead—have given negative results. Even Stockard, who unlike the other workers obtained malformations among the offspring of treated guinea-pigs, does not claim that the treatment has produced real mutations. On the whole I think Muller is perfectly justified in stating that there is no sound evidence for the belief that alcohol and other chemicals cause heritable changes. And I do not think that the recent results of Agnes Bluhm, based on 32,000 mice,

change this situation. The theoretical interpretation of the alleged mutation obtained is very artificial and devoid of parallels in more controllable experimental material.

At any rate, *there are not revealed in this field any general biological principles which are consistent and clear. And as long as this is the case we are not justified in drawing conclusions concerning man merely by analogy,* least of all here since the dosage and prolonged administration of alcohol in most experiments entirely surpasses any possible consumption by human beings. It even happened in the experiments that animals were made so dead drunk, by injection or inhalation, that they were eaten by the untreated animals with which they were expected to mate.

That a tendency to alcoholism in certain families may occasionally depend upon a hereditary weakness of character, which causes a lowered resistance to temptations in general, is of course a different matter. But in judging such cases of apparent hereditary transmission of alcoholism it should be remembered that perhaps in no other field are misconceptions so apt to arise, since the bad environment in the drunkard's home, the bad example during infancy, etc., is very likely to "contaminate" some of the children, in which

case an example of pseudo-inheritance is immediately established.

8. IS CANCER INHERITED?

IN another field of the foremost interest, the question as to the influence of heredity on the occurrence of cancer, the evidence is as yet rather limited.

In Drosophila, Bridges and Miss Stark have discovered both benign and malignant pigmented tumors which are caused by single autosomal or sex-linked recessive genes (see Text-fig. 32, p. 142). An interesting example may be quoted from horses which have the dominant gene for gray color. The colts are born with colored coats, but with increasing age, just as in old human beings, the new hairs turn gray. Hand in hand with this progressive depigmentation there occur true pigmented spindle cell sarcomas around the natural body openings, under the scapula and in the axillary glands (Plate XV, Fig. 58). The clear-cut dominance of this gene is strikingly illustrated by the Arabian stallion Amurath in Halle who was sire to no less than 900 foals, every single one gray.

Modern cancer studies have emphasized the importance of the local irritation in the pathogenesis of malignant tumors. Much evidence does seem to indicate that tumor formation is a function of two sets of

influences, the irritation on one hand, and the individual mode of reaction, or the susceptibility, on the other. That the latter factor may be governed by a simple Mendelian gene is illustrated by *Xeroderma pigmentosum* where, due to the hereditary constitution of the skin, ordinary sunlight causes deleterious cancer development in the exposed regions in childhood (Plate XV, Fig. 59), and also by the hereditary *polyposis adenomatosa* which favors the development of cancer of the large intestine. The Mendelian inheritance of *glioma retinæ,* an eye tumor, of *cartilagineous exostoses* and of *multiple neurofibromatosis* (Plate XVI, Fig. 60) are further examples of inherited susceptibility to formation of tumors.

In comparison with such cases the statistical evidence on high tumor incidence in particular families, as for instance the Bonaparte family, is generally of less value due to faulty diagnosis and to the lumping together of unrelated tumors. Quite a few of these alleged cases may also simply be due to coincidence, since 10 per cent of all individuals die from cancer.

The evidence from twin pathology which is more reliable supports the conception of a certain hereditary susceptibility. Krantz in a review of the literature records concordant cases of *adenocarcinoma uteri, fibroadenoma* of the left breast, *cancer of the*

larynx and *sarcoma* of the right *testis* in identical twins. On the other hand, clear cases of discordancy, only one of the identical co-twins being affected, are not infrequent, even in cases where both twins are well beyond the cancer age, a fact which demonstrates that an additional causative agency is usually involved.

This conception is also strengthened by the experimental evidence of Strong, Miss Lynch, Maude Slye, and others, working with different malignant tumors, especially in rodents. Different strains show different cancer incidence due to differences in the hereditary susceptibility. That this does not apply to spontaneous cancer formation only is demonstrated by the data of Kreyberg which bring out the very different times of onset of the skin tumor formation in two different, closely inbred strains of mice which were subjected to tar application. For one strain the first tumors appeared on an average around the third month, in the other around the seventh-eighth month. In this connection the observation of Loeb and Lathrop that the hereditary tendency to cancer of the breast in mice presupposes the activity of the internal secretion of the ovary —in genetic terms an external agency—is very interesting.

The hereditary mechanism of tumor susceptibility has not been determined with any degree of certainty.

At any rate, it cannot be as simple as supposed by Maude Slye on the basis of quite inadequate evidence. Moreover, even though we knew the hereditary type in detail, this would not tell us anything about how a normal cell is transformed into a cancer cell.

It is here that many scientists, among them particularly Bauer and Schinz, have advanced the hypothesis that cancer is a somatic mutation. We remember how a somatic mutation in a particular cell may lead to the formation of a mosaic area with characters that differ from those typical of the surrounding tissue (cf. p. 106). From experimental genetics (Demerec, Sturtevant) we even know genes that favor the occurrence of particular somatic point or chromosome mutations. It is not unlikely that somatic mutations may be the cause behind cases like those of *hemi-gynecomasty* or *hemi-chondrodystrophy* presented in Plate XVI, Figs. 61 and 62. But the somatic mutation theory of *tumor* formation can as yet hardly be regarded as more than a guess. Its advocates, as did first Boveri, point especially to the striking chromosome irregularities encountered in dividing tumor cells. Thus, to quote a single example, Winge and others have shown that the crown gall, a malignant tumor in the sugar beet that is induced by a microörganism, the *bacillus tumefaciens,* to a large extent consists of tetraploid cells, i.e., cells with the

double chromosome number of the species. Hansemann, in his cancer theory, believed the irregular divisions of the hyper- and hypochromatic cells of human cancer tissue to be diagnostic of malignancy.

But just this *irregularity* of the chromosome equipment in cancer cells seems difficult to bring into accord with the somatic mutation theory of cancer development. Modern cytological work (e.g., Levine, Alexenko, Anders, Kemp) shows that normal diploid cells, sub-diploid cells, and the most irregular polyploid cells up to real giant cells with an enormous number of chromosomes may occur in one and the same tumor, whether spontaneous or induced, e.g., by tar application or tumor-producing infestations. Thus Levine finds this relation to hold for human cancer tissue, Rous' chicken sarcoma, a tar tumor and a spontaneous tumor in the mouse, Jensen's rat sarcoma, as well as for crown gall tissue in the garden beet and in tobacco.

Nevertheless, both in the individual organism and when transplanted, each tumor exhibits an astonishing degree of constancy and specificity. As will be understood from our earlier consideration of the chromosome mechanism of gene distribution, this pronounced uniformity of the tumor tissue as regards general phenotypical characteristics is just the opposite of

what we would expect from the exceedingly variable chromosome relations of the tumor cells. It seems more likely that the chromosome irregularities are a consequence of the change that has occurred in the cancer cell rather than its cause. On the whole I fear that in the somatic mutation theory of cancer development we are dealing with rather superficial conclusions from analogy which hardly lead us any further as long as our knowledge of the growth and cell differentiation processes proper is as limited as it is to-day.

CHAPTER V

SOME BEARINGS OF GENETICS ON HUMAN AFFAIRS

WE have tried to acquaint the reader with the fundamental laws of heredity and their underlying mechanism. The essential feature of the mechanism is *segregation,* the basic fact that crossing of individuals of different genotype does *not* lead to blending or to gradual fusion into an intermediate type. Hereditary factors which meet in one individual disjoin and *segregate* again when his germ cells ripen, without having had the slightest modifying influence upon each other. The individual genes remain unchanged.

This gives us an answer to the double question involved in the problem of heredity. It explains not only why parents and offspring may show striking resemblances, but also the reasons for dissimilarities between them. If the maturation of the germ cells and the fertilization process did not intervene between two suc-

ceeding generations, parents and offspring would be completely alike. That this is the case is easily understood if we consider the situation in cases of asexual propagation, as for instance propagation by grafting or by cuttings. Our different commercial varieties of garden roses, for instance, are originally obtained by crossing. But a valuable variety, having been once secured in this way, is propagated on by grafting. Consequently, all roses belonging to this variety are descended from the original individual by ordinary cell divisions only. They are accordingly all of the same genotype and strikingly like each other.

But if a fertilization process intervenes between the generations, as is the case in sexual reproduction, then —and only then—are we confronted with the fascinating double play of heredity. The law of segregation and the stability of the genes explain on the one hand why special characteristics, e.g., the prominent lower jaw of the Hapsburg family or special traits of physiognomy characteristic of particular races, in spite of repeated cross-breeding, are retained through generations with remarkable constancy. On the other hand they also make us understand why children may differ strikingly from their parents, both in physical and mental respects. The gene combination typical of each parent is dissolved again when the germ cells develop.

In the offspring the parental genes will meet in a new and different constellation. A genius does not beget children of equal brilliancy.

Intermarriage and Cross-breeding

A series of fundamental problems has, thanks to our modern knowledge of heredity, come into an entirely new light. This applies, for instance, to the old question of *inbreeding*. There is a widespread popular belief that *intermarriage,* e.g., marriage between first cousins, is to be advised against, since occasionally unfavorable results are seen. On the other hand there is ample evidence, also in human material, that intermarriage has no harmful effects at all. As historical examples of very close inbreeding in man, the brother-sister marriages among the Ptolemaic family of old Egypt as well as among the Incas of Peru and the Aztecs of Mexico may be mentioned.

This question is of foremost importance, and an enormous amount of experimental work has been devoted to its solution. The result of these investigations may be summarized thus: inbreeding as such has no harmful effects at all. On the contrary, the astounding progress within animal breeding has been mainly based upon close inbreeding among the offspring of a limited number of prominent sires. In this way we are

able to "recapture" as many valuable genes as possible of those carried by the prominent sire in question. *Valuable* genes, this is the nub of the problem. If an undesirable recessive gene happens to be present within the family strain beforehand, then inbreeding will favor the occurrence of individuals that receive the undesirable gene in double dose, in which case the corresponding harmful character will come to light. The unfortunate results sometimes seen in consanguineous marriages are in other words not due to inbreeding as such, but to the presence of undesirable recessive genes in heterozygous condition in the antecedents of the family. Conversely, if the hereditary factors in the family are good, then even close inbreeding will give valuable offspring.

Degeneration

Inbreeding has frequently been blamed for causing "degeneration" of entire families or even races. The term "degeneration" deserves a more thorough elucidation than we are able to give it here. It is a very vague and indefinite expression, a slogan from a time when the laws of heredity were unknown. But it never fails to impress an uncritical audience. From a biological point of view the term would indicate that genes under special conditions are subjected to a gradual

decrease in value. We know perfectly well that nothing of the sort takes place.

Old families of nobility, for instance, are said to "degenerate," to die out. If we look somewhat deeper into the matter this proves to be a crude fiction. The family line has simply reached a point where no more *male* family members exist, so that the family is propagated through female members only. The paternal line, which transmits the family-name, has come to an end. And when the family-name, this biologically insignificant label, is lost, the family is said to have died out, irrespective of the fact that hundreds of individuals exist which descend from *female* family members. Genetically it is, of course, completely irrelevant whether the genes are transmitted through male or female members. *One of the most far-reaching achievements of modern biology is the definite establishment of the fact that men and women are genetically equivalent.* Even the genes for specifically male traits of form or behavior may just as well be inherited from the mother.

Race Crossing

Race crossing has also been blamed as a cause of "degeneration" of peoples or even of entire races. It is only too obvious that back of most of these frightening

pictures of race deterioration motives are found, conscious or unconscious, that have nothing to do with science. Just at a time when genetics has entered the era of an exact science, unscrupulous propagandists who lack the most elementary genetic training pose as experts and mislead the public. Shocking descriptions of the imminent danger of race deterioration are accompanied by constant appeals for protection of the "pure race," and warnings against any intermingling with other, invariably "inferior" races. And everywhere uncritical writers, who believe themselves to be Nordic, outbid each other in eulogies of the marvelous inborn qualities of the so-called Nordic race. It has been a repulsive spectacle, and the tragic consequences of this thoroughly unscientific appeal to prejudice and snobbery are seen in Europe to-day.

It may be worth while in this connection to quote an authority like T. H. Morgan: "Whatever advantages some kinds of pure races may have from a political, religious or militaristic viewpoint, this should not blind us to the possibility of the biological advantages that certain mixtures may bring about." As a matter of fact, *in civilized humanity where crossbreeding prevails, pure races do no longer exist.* To quote another first-rate authority, W. Johannsen, the exponent of the pure line principle: "From the point of view of a

pure-bred dog, we are all curs." But be it understood that for *general* purposes a cur is on the whole much more valuable than most of the pure bred races. The Pekingese may give pleasure to elderly ladies, and the bulldog may compensate inferiority complexes in some gentlemen. But these are *special* purposes. The word "pure" does not involve general superiority, as we are apt to assume from the mere sound of the word.

The Blue Blood

Some people are proud when they are able to trace their pedigree back to the portrait of a remote ancestor. From a genetic point of view such "pedigrees" are rather comic. Disregarding possible cases of intermarriage, we have already 64 ancestors in the sixth generation. What does it matter to know one of these, when the rest, the 63 unknown ones, are genetically equally important? If we go the other way, trying to construct family trees comprising *all* our ancestors, we do not get far back until we meet persons who, both in personal and social respects, would be regarded as rather undesirable relatives by the present bearers of the family name. Such an investigation is not apt to promote our respect for the so-called "blue blood."

On the whole, persistent misconceptions are widespread in the fields with which we are dealing. Some

of them even have nothing to do with heredity. This applies for instance to the belief in *telegony,* after-effect, which even Darwin shared. Dog-breeders have been particularly prone to this belief. It is thought that a bitch that by accident has been mated with a male dog of another breed is spoiled, useless for future pure breeding. Now when we know the mechanism of fertilization it needs no explanation that this belief is entirely absurd. Mating, and the fact that a litter of mixed breed has stayed temporarily in the uterus of the bitch has of course not the slightest influence on the germ cells present in her ovary and the genes which they contain.

Maternal Impressions

More serious in its consequences is the old deep-rooted belief in *"maternal impressions"* which has caused much unfounded self-reproach among conscientious mothers. Everybody has probably met with the popular conviction that if a pregnant woman happens to see the head of a hare, there is imminent danger of the coming child developing harelip, or even cleft palate. Birth-marks are traced to burns acquired by the mother, in corresponding locations, and temperamental deviations in a child are attributed to the mother's distress or loss of temper during pregnancy.

Conversely, I know of a case in which a husband systematically took his newly married wife to fine concerts in order that the expected child might be musical in contrast to the parents. No wonder that he was badly disappointed at the results of this treatment.

One might expect that it would be comparatively easy to persuade people that external influences of this sort do not penetrate deeply enough to produce changes in the child, which, as an independent individual, happens to spend the first nine months of life as a parasite within the mother's body. But as a matter of fact, according to my experience, it is exceedingly difficult to persuade the parents that the fate of the child in these respects is irrevocably determined already at fertilization, when the two germ cells meet. So in dealing with this question I have frequently been forced to resort to the following argument: "Well, what do you think your child would look like, if all the external impressions to which you are exposed during the nine months of pregnancy really left traces in the development of your child?"

Are We Able to Rationalize Human Breeding?

One of the most important deductions from our knowledge of the laws of heredity is the fact that a judgment based on external inspection only is insuffi-

cient and frequently directly misleading when it is a question of deciding whether an individual is genotypically valuable or not. It is by no means certain that a good working animal is a good breeder. Who can say what is under the skin? In plant and animal material, however, we are able to obtain information on the genotypical constitution of an individual by aid of breeding tests. And we may improve races by selective mating of individuals which transmit the desired traits, and by eliminating unfavorable offspring. Hence in plants and animals our knowledge of the laws of heredity has indisputable bearing on practical breeding.

The inference is therefore tempting that by proper application of genetic principles in man we might also rationalize human breeding. But here we are up against very considerable, almost insurmountable difficulties. Clearly, in some cases where we know the gene for a particular dominant pathological condition, we may stop its further transmission by preventing the affected individuals from propagation. But this negative procedure is very limited in scope. Not only are a great many dominant pathological states in man incompletely dominant, so that normal-looking heterozygous carriers escape detection, but the large majority of in-

jurious genes are recessive, and in this case *all* the heterozygous carriers are perfectly normal.

In the modern community crossbreeding and the contra-selective methods of medicine may to a certain extent neutralize the tendency to elimination of deleterious genes that is brought about by the merciless natural selection in free nature. And it is not to be doubted that undesirable genes are relatively widespread in the human population, just as they are apt to be in any cross-bred group, a situation that is well illustrated by the experimental evidence from maize. But in dealing with recessive pathological traits it is of very little importance to prevent the few homozygous affected individuals from propagation. The gene will continue to spread through heterozygous, normal carriers.

Sterilization

In the United States, up to 1933, about 16,000 persons had been sterilized because they were for different reasons considered unfit for propagation. But an American committee estimated that no less than 15 million persons ought to be sterilized up to 1980, starting with 100,000 a year and increasing the number up to 400,000 annually. Lenz in Germany regards 10 per cent in each generation as a by no means too high percentage of sterilization. But he even regards "ausge-

sprochene Hässlichkeit," pronounced ugliness, as a proper indication for this procedure!

The effect of sterilization is at best very, very slow. To take a single actual example (after Hogben): One of the best known recessive pathological traits in man is ordinary albinism, lack of pigmentation of skin and eyes. This anomaly has an incidence of less than $\frac{1}{100}$ per cent. If sterilization of all albinotic individuals was carried out in every generation, it would require a period about equivalent to the Christian era to reduce its incidence to one-half of its present dimensions, a simple consequence of the fact that the heterozygous carriers continue to transmit the gene.

These examples are not quoted as arguments against sterilization proper. Its application is advisable not only in the relatively few cases in which by this method we may prevent dominant defects from being transmitted to the offspring, but also because irresponsible defectives like imbeciles or schizophrenic individuals are entirely unfit to serve as parents and educators of children, even though we cannot predict that their children will be similarly affected. There is moreover every reason to object to the uncritical enthusiasts who in all countries mislead the public by giving a wrong impression of the effectiveness of the measures recommended. It should also be remembered that in

several cases, as for instance in schizophrenia, the fecundity of the affected is by itself so reduced that, as Nissen's statistics from Norway show, we must assume repeated mutations of the causative genes in order to account for the fact that schizophrenia has not been eliminated by nature's own virtual sterilization of the affected. On the whole, those who are affected with really serious hereditary abnormalities do not propagate at a rate that is sufficient to keep up their number.

Animal Breeding Versus Human Breeding

If the negative measures for genetical improvement of the human population are limited in scope, the difficulties are insurmountable when it comes to the question of improving the population by positive measures. The frequent reference to the unquestionably good results of applying genetic principles in animal breeding is entirely misleading. The progress within animal breeding is due to methods which are entirely out of the question in human material, viz., close inbreeding and rigid elimination of all undesirable individuals. By this procedure latent hereditary defects are intentionally brought to the surface so that homozygous affected individuals may be eliminated without mercy. Moreover, in plants and animals we have *definite goals* at which the breeding aims, e.g., milk production in cattle, speed

in horses, and so on. But what types should be preferred among human beings, the intellectual or the athletic type, only to mention two possibilities? And to whom should the responsibility of this decision be delegated? These are questions that nobody is able to answer.

As matters stand, the actual breeding principles in man lead to the production, not of relatively uniform standard types, but to a rich variety of very different types. And, on the whole, this undoubtedly represents an advantage in a civilized community. Highly differentiated civilized life needs a wide spectrum of types. Many individuals, who from one point of view may be considered inferior, and who in free nature would have no chance of survival, may *in a civilized community* range among the most prominent personalities by virtue of special abilities which here, and *only* here, may come into their rights. In the English thoroughbred horses the simple recessive inheritance of blood vessel breaking has been conclusively demonstrated by Robertson. The two Derby-winners, Hermit and Humorist, suffered from this disease. One of them suffered from a serious hæmorrhage one week before his victory in a race, the other died 17 days later from a broken blood vessel. The famous sire Gallinule was also a bleeder and was for this reason a failure in races.

Nevertheless he was one of the leading sires within the breed. "Gallinules are always stayers" runs the slogan in Ireland to this day.

Birth Control

It is frequently stated that the widespread application of contraceptive methods will lead to "race suicide" by lowering in a selective way the productivity of the best germinal material. The advocates of this view simply take it for granted that the best germinal material is represented by the "good families," the upper social strata, among which *birth control,* as is well known, has been most generally applied.

If this view is correct the upper classes would, so to speak, have attained their favored position by natural right, by virtue of their superior genotypical quality, a conception that has been illustrated by the following metaphor: The population is compared to a container filled with milk, a fluid in which larger and smaller fat drops are dispersed. After a while these drops of fat will float to the surface, and the largest, fattest drops of fat will form the upper layer of the cream, the *crème de la crème* of the French.

From a biological point of view this metaphor is entirely misleading. Let us assume that a particular individual, due to his superior genotypical equipment,

has been able to fight his way from the proletariat to the propertied class. Here he marries. There is nothing to guarantee that his wife will be on an equally high level genotypically. Moreover, when his germ cells ripen, segregation, the very principle of Mendelian inheritance, insures that this valuable combination of genes is again dissolved, and his genes will enter new combinations in the children. These children may very well be quite ordinary as regards their genotypical quality.

But, thanks to better nourishment, better opportunities and training, it is much easier for individuals born in an economically independent upper class environment, even though genotypically mediocre, to remain on the social level of their parents, than it is for an individual of superior genotype to overcome the handicap involved in an unfavorable environment with limited opportunities. In a crossbred population like the human one, we may be fairly sure that good and bad germinal material is scattered pretty much at random among the different social strata.

If this is true, this argument against birth control loses its weight. At any rate, an appeal to the intelligent and responsible circles to effectively increase their number of children is futile. The only way open in order to counteract an assumed selective birth rate

is accordingly to spread the same information among the poor, not for fear of their inferior genotypical quality, but because every child ought to develop in a good environment. And this goal cannot be attained if we give natural fertility its free course.

The Attitude of the Physician in Questions of Heredity and Disease

The individual medical practitioner is most frequently consulted as to the possible consequences of marriage in cases where one or even both partners belong to a family in which pathological hereditary traits occur. Provided he is really familiar with the mechanism of segregation of autosomal and sex-linked traits and has grasped the essentials of dominant and recessive inheritance he may, by aid of one of the now existing text-books on the known pathological hereditary traits in man, give valuable advice in quite a few cases. But his judgment should always be given with the reservation involved in the fact that genetics primarily deals with probabilities.

It is from the trained medical man that further progress in our knowledge on the inheritance of disease conditions in man is to be expected, since he is likely to encounter new cases and only he is able to give the exact diagnosis on which everything depends. A thor-

ough study of a limited amount of material is worth more than the accumulation of statistics regarding hundreds of less accurately controlled cases. It should also be remembered that it is just as important to examine all the normal family members as it is to investigate those who are said to be affected. As a rule, not much reliance may be placed on indirect information. For the interpretation of the carefully collected data on normal and affected family members it may eventually be advisable to consult a trained geneticist. But the collection of really reliable data is the main point. Here is a wide field, and a very fascinating field, too, for the medical man who is not satisfied with the mere routine work of his profession.

A frequent question is whether a normal person belonging to a family in which a recessive pathological trait occurs may be expected to beget affected children if he marries an unrelated individual. This must of course be answered in the negative. As regards serious dominant abnormalities we have presented quite a few cases where affected heterozygous carriers should be advised against propagation, even though the chance of begetting an unaffected child is 1 : 1. If such an individual nevertheless takes the chance and begets a normal child, then further propagation should be prevented.

We have also explained (p. 61) why intermarriage in families where dominant pathological traits occur is generally inadvisable. In families where serious recessive pathological traits are met with, such as extreme eye abnormalities and hereditary types of deafness, the risk involved in an intermarriage of two normal, but possibly heterozygous family members should be made clear to the consultants. If they prefer to take the chance, which is at worst 3 : 1 in favor of begetting a normal child, I advise against further propagation if the first child is normal.

But we are here dealing with human fates and must consider the individual. In my own experience a woman gave birth to a child suffering from a recessive lethal type of infant paralysis. After I had explained the probabilities to the parents, they decided once more to take the chance. To our great regret also this second child developed a fatal paralysis. But when they tried also a third time, they had a perfectly normal child. The fact that this hereditary lesion is absolutely lethal, paradoxical as this may sound, represents an advantage. The cases in which seriously affected children survive are much more tragic in their consequences.

As regards serious sex-linked anomalies, as for instance hæmophilia, I think affected men should be

strongly advised against propagation, since their normal daughters are sure to transmit hæmophilia to half their sons.

As will be realized, most of the measures outlined tend to prevent hereditary pathological states from coming to the surface. This brings the physician into the conflicting situation that his advice in the interest of the individual very frequently runs counter to the interests of the population, since it favors the further transmission of undesirable genes through unaffected heterozygous carriers. The same is true of our therapeutic measures in trying to alleviate the symptoms in the affected individuals themselves. It is of no use to hide this paradoxical situation which will prevail until perhaps a method is found by which we are enabled also to identify the heterozygous, normal carriers of recessive genes. So far nothing indicates that we are even approaching this goal.

Heredity and Environment

It cannot be denied that the establishment of the fundamental fact that the genes are virtually unchangeable by external agencies is somewhat disillusioning. All the valuable acquirements which conscientious parents may accumulate in the course of life are *genetically* a dead investment. Conversely, how-

ever, the same fact involves considerable consolation. Neither are our evil acquirements visited upon our children genotypically. Irrespective of the parents' dissipated manner of life the children may nevertheless in genetic respects get a good start, this start only depending upon the genes which the parental germ cells contained.

It is quite another matter, however, that the evil acquirements of the parents create a *bad environment* for the children. It is here that their fatal consequences are to be sought. Alcoholism, for instance, creates a bad environment, a bad milieu, for the children in almost every respect. Grave infections in the parents may lead to contamination of the children. The same holds true for moral dissipation.

We finish as we started by emphasizing that *each individual, each personality, is a product of two sets of influences, the genes on the one hand, the environment on the other.* Valuable genes may in a bad environment be hampered in their manifestation. Badly nourished dairy cattle give low milk production however valuable the genes which they carry for milk production and butter fat percentage. Conversely, a good environment may in many cases counteract and eventually suppress the influence of undesirable genes, and

effectively accentuate the manifestation of the valuable genes.

The following case may help to illustrate this fundamental relation: In Norway all schools, both lower and higher, are public schools. In Table II some data on stature and body weight are presented in Oslo school children, derived from the very complete statistics collected by the municipal school physicians.

As seen from this table there is a most remarkable general increase of stature and body weight in the course of the last ten-year period. It is perfectly clear that the genotypical quality of the population cannot have changed perceptibly during so short a time. The very striking change must be due to the improvement of environmental conditions, better hygiene, better nourishment, etc. The experts in their comments upon this evidence point particularly to the fact that the widespread application of birth control has reduced the size of the family very considerably. The number of births in Oslo was 4,900 in 1920, 2,100 in 1933. It is a matter of course that in small families each child will have much better care, i.e., much better environmental conditions, than will be the case in large families with correspondingly limited financial opportunities.

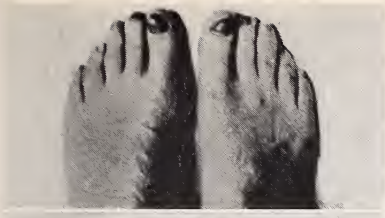
The conclusion to be drawn from the above is that

Age	Sex	Body height in cm.			Body weight in Kg.		
		1920	1930	Increase	1920	1930	Increase
10 Years	Boys	130.91	135.13	*4.22*	27.58	29.87	*2.29*
	Girls	130.02	134.59	*4.57*	27.02	29.79	*2.77*
14 Years	Boys	148.22	153.10	*4.88*	38.54	42.64	*4.10*
	Girls	150.60	154.94	*4.34*	41.81	45.50	*4.31*
14 Years	Boys	153.46	157.39	*3.93*	42.39	45.46	*3.07*
	Girls	154.91	158.52	*3.61*	44.92	48.10	*3.18*
18 Years	Boys	173.55	176.07	*2.52*	62.30	64.27	*1.97*
	Girls	161.64	164.69	*3.05*	52.87	56.94	*4.07*

TABLE II. *The ten-year increase of body height and body weight in Oslo school children, 1920–1930. Above the double line, pupils in lower public schools. Below the double line, pupils in higher public schools (grammar school, gymnasium).*

we must join in the attempts to create fair living conditions by correcting the internal and external environmental evils. We should also endeavor to give all children equal access to knowledge and information by the training of their abilities. By giving all individuals at the start as equal chances as possible, we make the struggle for life fair and enable the carriers of valuable genes, wherever they turn up, to win through to the full unfolding of their inborn capacities.

Even though we are aware that our efforts to improve the environment will have no influence on the genes themselves, we may still hope in this way to make the lives of men happier and promote the progress of humanity.



LEFT:
Fig. 1. Dominant onychogryphosis, horn-like nails, affecting the toe nails only. Hands and feet from the same individual.

RIGHT:
Fig. 2. Farabee's type of dominant brachgyphalangy, shortening of fingers and toes. FROM DRINKWATER.

Fig. 3. Gregor Mendel (second from right, upper row) in a group of his colleagues. FROM ILTIS.

Fig. 4. Dominant woolly and short type of hair in a nordic family. Mother and three children woolly. FROM MOHR.

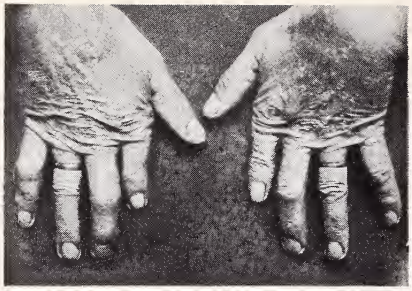


Fig. 5. Dominant brachyphalangy, shortening of the index fingers and second toes only. FROM MOHR AND WRIEDT.

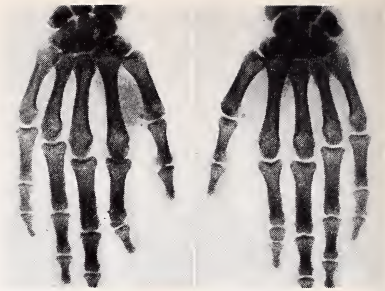


Fig. 6. Radiographs of the type of brachyphalangy shown in Fig. 5.

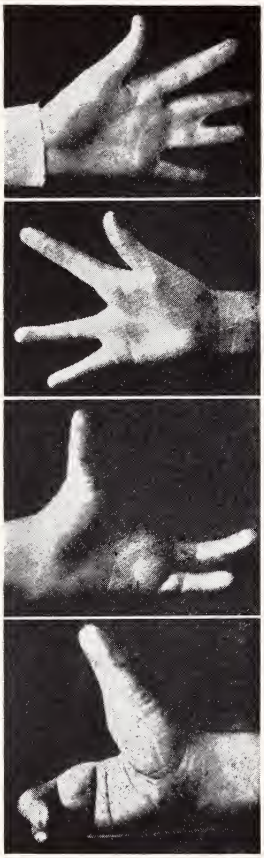


Fig. 7. Variable type of dominant syndactyly. Above, the hands from one; below, the hands from another family member. FROM SCOTT.

Fig. 8. Dominant malformation of hands and feet in mother and child. FROM BROMAN.

Fig. 9. Dominant absence of hands and feet. The man is the brother of the children's father, who was similarly affected. FROM PEACOCK EX FEDERLEY.

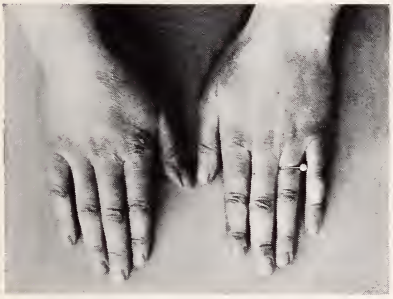


Fig. 10. Normal hands of the mother of an illegitimate child whose hands are shown in Fig. 11. FROM MOHR.

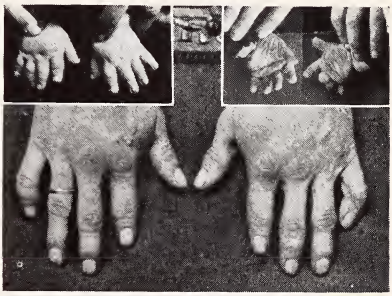
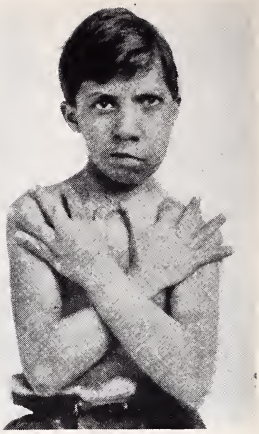


Fig. 11. Finger shortening in child of the woman, Fig. 10, and in the alleged father. FROM MOHR.

Fig. 12. Recessive universal albinism. Normal parents; three children albinotic. FROM PEARSON, NETTLESHIP AND USHER.

LEFT:

Fig. 13. Photographs of female Drosophila equatorial plates with chromosome aberrations. Above, an extra hook-shaped Y-chromosome seen upwards to the right. FROM GOWEN AND GAY. Below, one of the small round chromosomes lacking. FROM MOHR.



RIGHT:

Fig. 14. Congenital hemi-hypertrophy of left side of body. FROM BASSOF.

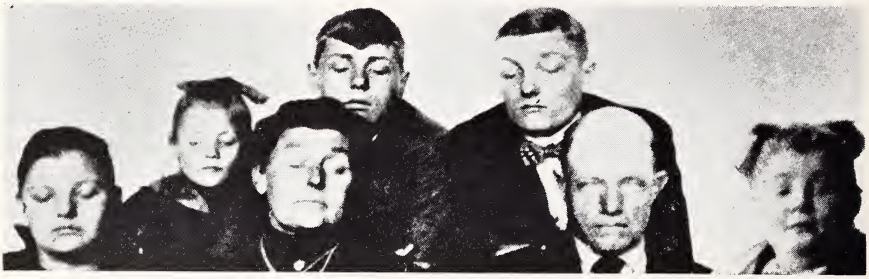


Fig. 15. Dominant ptosis, drooping eye lids. Mother and all the children affected. FROM FLIERINGA.

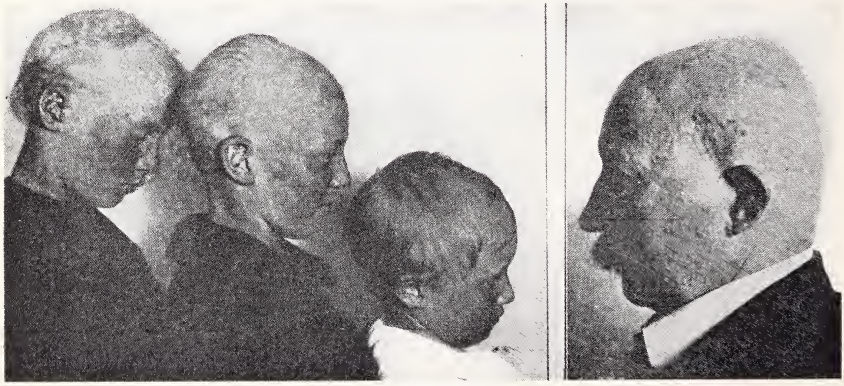


Fig. 16. Father and three sons with dominant juvenile type of hairlessness. FROM THOMSEN.

Fig. 17. Dominant dysostosis cleido-cranialis. Rudimentary collar bone, underdevelopment of subcutaneous fat, skull defects and abnormal osseous sutures. FROM YTTRI, AND HULTKRANTZ EX YTTRI.

Fig. 18. A "chromosome map" of the maize chromosomes with living mutant representatives of the respective gene loci. FROM PROCEEDINGS VI INTERNAT. GENET. CONGRESS.

Fig. 19. Cleft iris. FROM WAARDENBURG.

Fig. 20. Father and three children with "spider fingers" and lens luxation. FROM WEVE.

Fig. 21. The hands of the individuals shown in Fig. 20. Below to the left, a normal hand for comparison. FROM WEVE.

Fig. 22. Progressive degeneration of liver and basal ganglia of the brain, "Wilson's disease." FROM HALL.

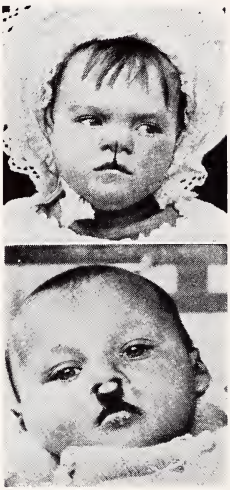


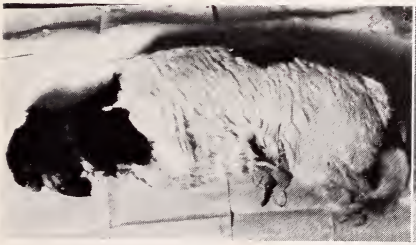
Fig. 23. Harelip, above; harelip with cleft palate, below. FROM RISCHBIETH.

Fig. 24. Achondroplastic "bulldog" abortion in Dexter cattle. Dominant gene with recessive lethal effect. FROM CREW.

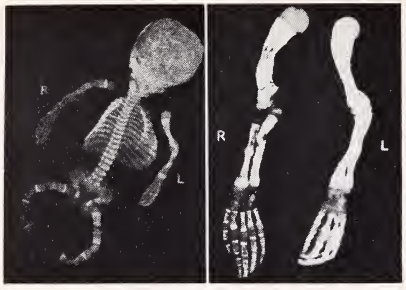
Fig. 25. Achondroplastic "bulldog" calf from the Norwegian Telemark breed. Recessive sublethal gene. FROM WRIEDT AND MOHR.

LEFT: *Fig. 26.* Lethal congenital contractures due to a recessive sub-lethal gene. FROM MOHR.
RIGHT: *Fig. 27.* Cranium of calf with anchylosis of lower jaw due to a recessive sub-lethal gene. FROM MOHR.

LEFT: *Fig. 28.* Congenital lethal hairlessness due to a recessive gene. FROM MOHR AND WRIEDT.
RIGHT: *Fig. 29.* "Elk-calf" due to malformation of spinal column (and ribs) induced by a recessive sub-lethal gene. FROM MOHR AND WRIEDT.



LEFT: *Fig. 30.* "Amputated" calf due to skeletal abnormalities affecting skull and skeleton of legs only. FROM WRIEDT AND MOHR.
RIGHT: *Fig. 31.* Congenital ichthyosis caused by a recessive lethal gene. FROM LESSER.



ABOVE: *Fig. 32.* Congenital type of osteogenesis imperfecta. Radiographs showing the pre-natal multiple fractures. FROM KNAGGS.

RIGHT: *Fig. 33.* "Amputated" abortion in man. The parents were first cousins. FROM MOHR.

Fig. 34. Conjoined or "Siamese" twins. FROM BROMAN.

Fig. 35. Double-monster. FROM BROMAN.

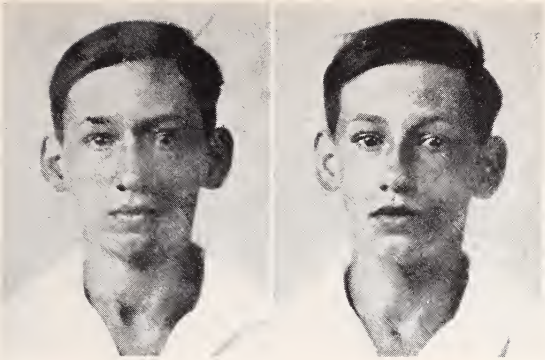


Fig. 36. Identical twin brothers. Note the outstanding ears in both. FROM QUELPRUD.

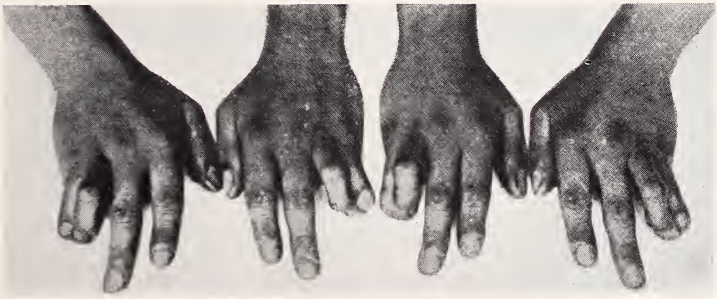


Fig. 37. Syndactyly in identical twins. FROM K. H. BAUER.

Fig. 38. Identical twin brothers with inguinal hernia. Note, the mirror imaging. FROM V. VERSCHUER.

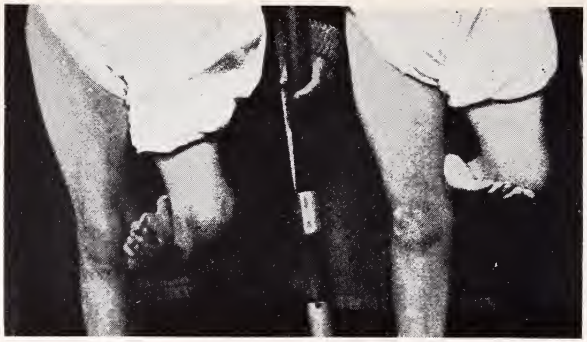


Fig. 39. Identical twin sisters with severe malformations of left leg and foot only. FROM OLLERENSHAW.

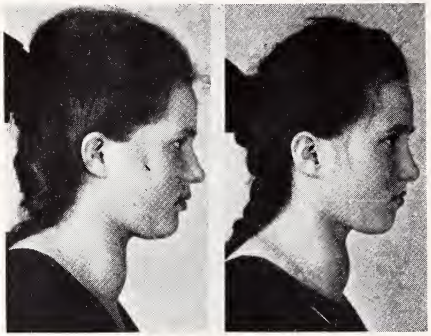


Fig. 40. Goitre in identical twins. FROM WEITZ AND V. VERSCHUER.

Fig. 41. Feebleminded identical twins. FROM J. C. SMITH.

Fig. 42. Feebleminded identical twins. FROM J. C. SMITH.

Fig. 43. Different stages of female intersexuality in Lymantria. Normal female above. FROM GOLDSCHMIDT.

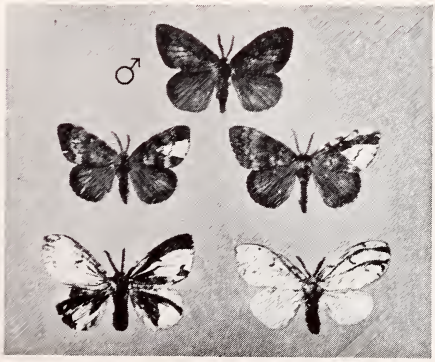
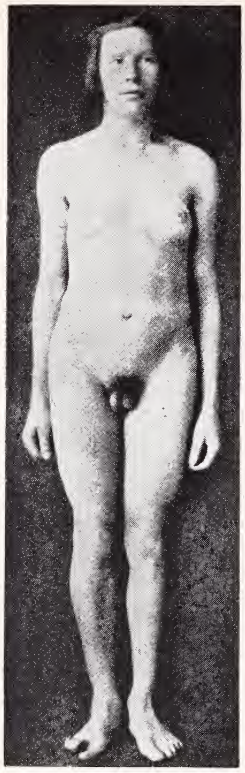
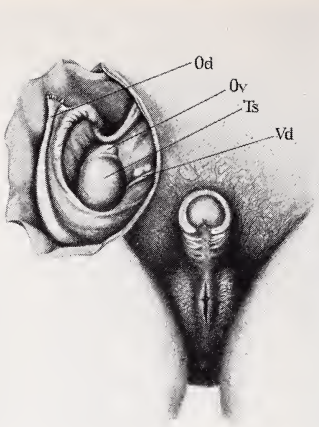


Fig. 44. Different stages of male intersexuality in Lymantria. Normal male above. FROM GOLDSCHMIDT.





A

B

LEFT: *Fig. 45.* Female intersexuality. FROM HALBAN.
RIGHT: *Fig. 46. A,* External and internal reproductive organs from female intersexual individual. Ov = ovarian, Ts = testicular part of the ovo-testis. Od, oviduct. Vd, rudimentary sperm duct. AFTER SIMON. *B,* Microscopical section through ovo-testis from female intersexual individual. To the left, ovarian tissue with egg follicles; to the right testicular tissue. SALÉNS CASE, FROM PICK.

Fig. 47. Identical twins with hypospadia, abnormal opening of urethra indicated by arrows. FROM VOÛTE.

Fig. 48. A hen that has changed into a cock. FROM CREW.

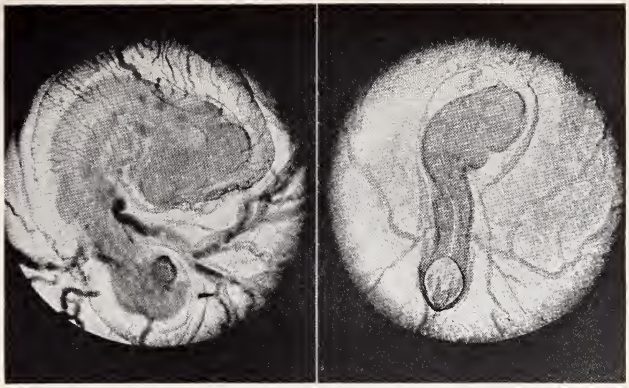
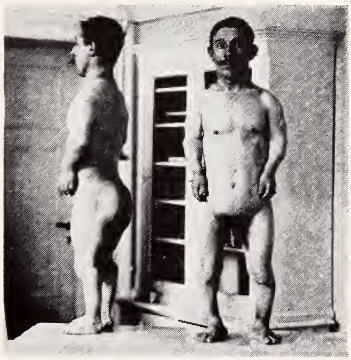


Fig. 49. To the left, normal embryo from Creeper parents, 72 hours of incubation. To the right, homozygous Creeper embryo, 72 hours of incubation. FROM LANDAUER.

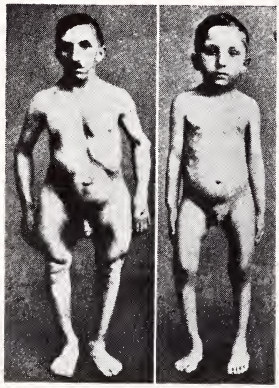
ABOVE: *Fig. 50.* Double-monster with cleft palate. FROM BROMAN.

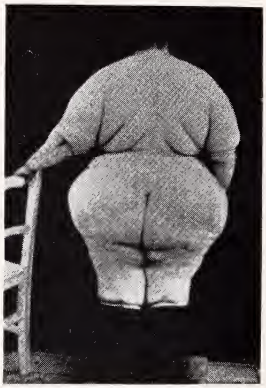
Fig. 51. Monster with brain hernia, cleft palate and polydactyly. FROM BROMAN.



RIGHT: *Fig. 52.* Chondrodystrophic identical twins. FROM SCHEMENSKY.

Fig. 53. Dwarf brother and sister with their normal brothers. FROM HANHART EX JUST.





LEFT: *Fig. 54.* Father and son with Osteogenesis imperfecta, abnormal brittleness of bones. AFTER ZONDEK FROM SALLER. RIGHT: *Fig. 55.* Woman with adipositas. AFTER J. BAUER FROM SALLER.

Fig. 56. Bulldog and bulldog-like man. FROM STOCKARD.

Fig. 57. Pekingese and Pekingese-like human dwarf. FROM STOCKARD.

Fig. 58. Horse with dominant gray color; pigmented tumors around the anal opening. FROM WRIEDT.

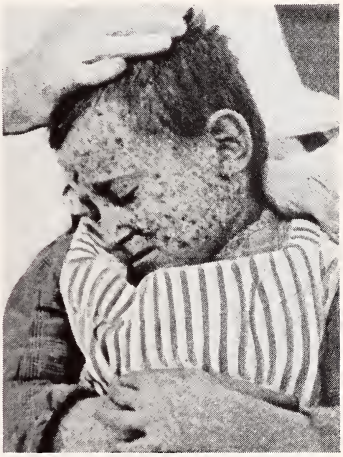


Fig. 59. Xeroderma pigmentosum. FROM RIEHL-ZUMBUSCH.

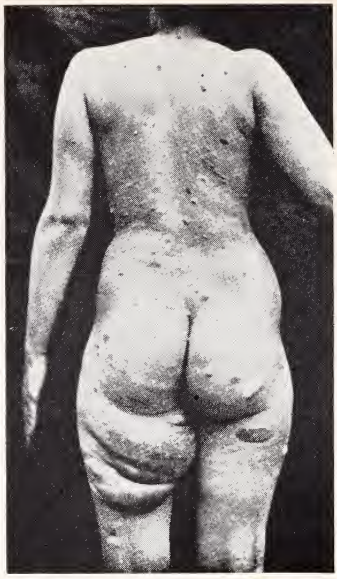


Fig. 60. Multiple neurofibromatosis. FROM HARBITZ.

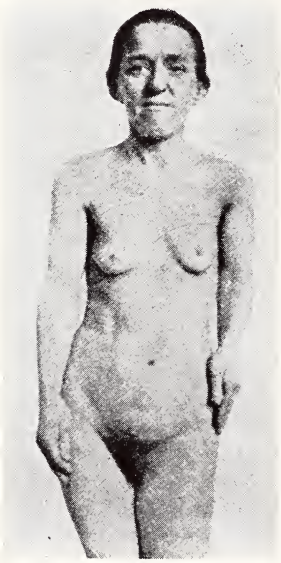


Fig. 61. Chondrodystrophy of left arm only. AFTER J. BAUER FROM JUST.

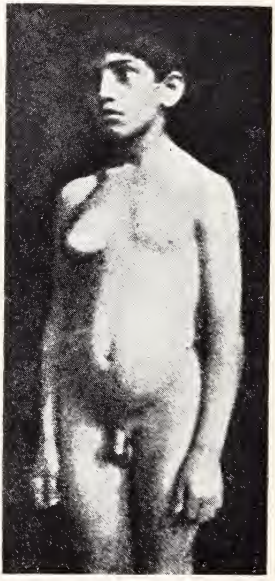


Fig. 62. Gynecomasty of right breast only. AFTER J. BAUER FROM JUST.

APPENDIX

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